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SURGICAL IMPORTANCE OF MAMMARY AND SUBCUTANEOUS FAT NECROSIS

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A thorough knowledge of the pathogenesis and clinical manifestations of fat necrosis is of considerable surgical importance because all too frequently the similarity of this condition to cancer has led to ill advised surgical intervention or irradiation therapy. This is particularly true of fat necrosis in the breast, despite the accurate description of this condition as a clinical entity over a decade ago.[1] However, fat necrosis may prove to be equally baffling or even more so when it occurs in a mastectomy scar, in a lipoma, in a hernial sac or deep in the subcutaneous tissues of the thigh or the buttock. It is the purpose of the present paper to call attention once again to the inherent difficulties in recognizing this condition and to emphasize its importance in the differential diagnosis of malignant lesions in the breast or of the superficial tissues.

One of the earliest descriptions of extra-abdominal fat necrosis was that of Shattock, who in 1896 described an occurrence of "saponifying necrosis" in a lipoma of the thigh. Since that time the condition has been described under a number of titles, of which the most familiar are "traumatic fat necrosis,"[1] "ischaemic fat necrosis"[2] and "lipogranulomatosis."[3] Since fat necrosis is not a true granuloma and since it may occur independently of proved trauma or ischemia, it seems better to designate it according to its anatomic location as "mammary" or "subcutaneous" fat necrosis.

Usually fat necrosis appears as a solitary lesion, but its lesions may be multiple, especially in the newborn. In such patients it must be distinguished from sclerema and scleroderma neonatorum. It is a well

From the Surgical and Pathologic Services of the Peter Bent Brigham Hospital.

1. Lee, B. J., and Adair, F.: Traumatic Fat Necrosis of the Female Breast and Its Differentiation from Carcinoma, Ann. Surg. **72**:188 (Aug.) 1920.

2. Farr, C. E.: Ischaemic Fat Necrosis, Ann. Surg. **77**:513-523 (May) 1923.

3. Harbitz, H. F.: Lipogranuloma—Foreign Body Inflammation Often Suggesting Tumor, Acta chir. Scandinav. **76**:401-426, 1935.

defined entity; it is almost certainly the result of trauma; and in contradistinction to scleroderma neonatorum it has a uniformly good prognosis.[4] In the adult, multiple areas of fat necrosis are of rare occurrence, but they have been described as following infectious diseases.[5] It is possible that such multiple areas of fat necrosis are the result of ischemia due to vascular lesions. Christian-Weber's disease is included in this classification by some authorities.

It is with the solitary lesions of fat necrosis, however, that the surgeon is particularly concerned. The exact factors involved in the development of this condition have not been established. The lesion may arise after trauma, after the injection of foreign material, especially fats and oils, after interference with the blood supply to a part or after infection. However, if any of these factors alone is sufficient to produce fat necrosis it is difficult to understand the comparative rarity of the lesion when one considers the frequency of trauma to, and infection in, subcutaneous fat. It seems likely, therefore, that in addition to these various exogenous factors an endogenous factor is essential for the production of fat necrosis. The nature of this endogenous factor is hypothetic, but it may be a blood or tissue lipase[6] which is more abundant or more easily activated in certain persons than in others.

In evaluating the experimental production of fat necrosis as well as in diagnosing the condition of pathologic material it is well to bear in mind that fat splitting and fat necrosis may be separate processes which, although usually closely allied, are not necessarily so.[2] Thus, the presence of fat crystals alone is not sufficient histologic evidence to warrant a diagnosis of fat necrosis. Also, after the injection of foreign material, especially fats and oils, an intense foreign body reaction may be observed; such a reaction is not necessarily fat necrosis. In certain cases this foreign body reaction becomes a progressive lesion which possesses the essential histologic features of fat necrosis. That this is not always the case, however, can be seen in figure 1, which represents the reaction produced by injection of cod liver oil into the peritoneal fat of a guinea pig. It should be noted that although there is a marked foreign body reaction the adjacent fat appears normal. It should be noted also that there is no actual necrosis of fat with the formation of confluent polyhedral spaces much larger than a normal fat cell, such as is seen in figure 2. This dissolution of normal fat cells into confluent

4. Fox, H.: Subcutaneous Fat Necrosis of the New-Born: Report of Five Cases, Arch. Dermat. & Syph. **27**:237-252 (Feb.) 1933.

5. Abrikossoff, A.: Ueber die spontan auftretende Fettgewebsnekrose und Fettgranulome, Centralbl. f. allg. Path. u. path. Anat. **38**:542-546 (Nov. 15) 1926; cited by Harbitz.[3]

6. Neal, M. P., and Ellis, M. M.: Etiological Factor of Fat Necrosis, South. M. J. **23**:313-320 (April) 1930; Experimental Fat Necrosis in Various Vertebrates, Am. J. Clin. Path. **1**:251-263 (May) 1931.

spaces seems to be an essential characteristic of true fat necrosis. It apparently represents one of the earliest histologic changes. Within these spaces are the products of the decomposing fat, which usually excite a mild but slowly progressive foreign body reaction. This is characterized chiefly by an infiltration of mononuclear phagocytes,

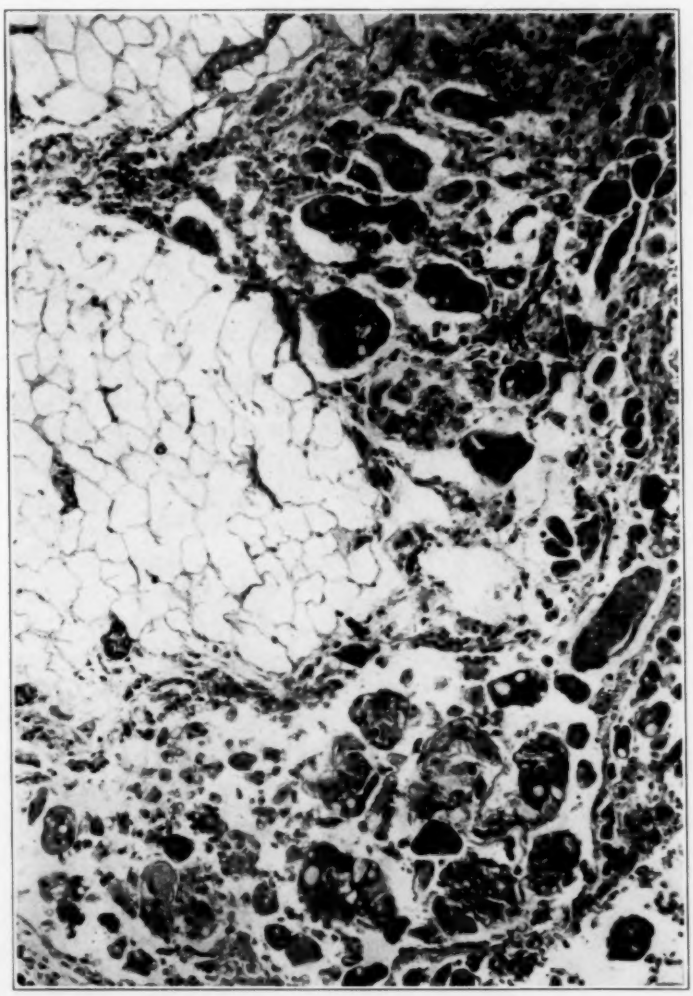

Fig. 1.—Photomicrograph (× 165) of the peritoneal fat of the guinea pig ten weeks after the injection of cod liver oil. Note the intense foreign body reaction without the formation of confluent spaces or vacuolated areas in the adjacent fat. Compare with figure 2. (The specimen was stained with eosin and methylene blue.)

many of which become filled with particles of necrotic fat. These so-called "foam cells" are found about the periphery of the broken-down fat (fig. 3). This is followed by proliferation of the surrounding

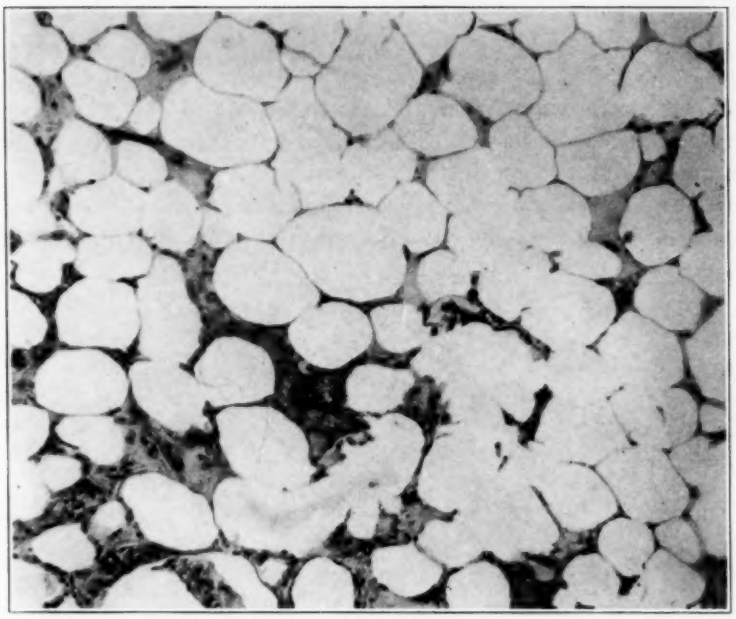

Fig. 2.—Photomicrograph (× 90) showing the early changes of fat necrosis. In contrast to figure 1, in this tissue one finds irregular polyhedral spaces much larger than a normal fat cell. The formation of these confluent cystlike areas seems to be an essential histologic characteristic of fat necrosis. (The specimen was stained with eosin and methylene blue.)

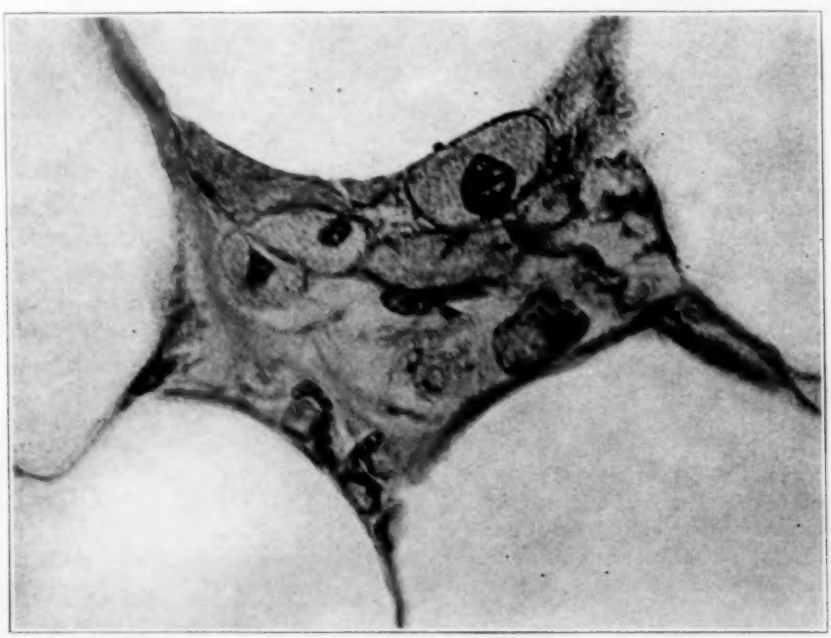

Fig. 3.—Photomicrograph (× 900) showing the cellular reaction in early fat necrosis. The large mononuclear phagocytes are filled with the products of the decomposing fat, constituting the so-called "foam cells." (The specimen was stained with eosin and methylene blue.)

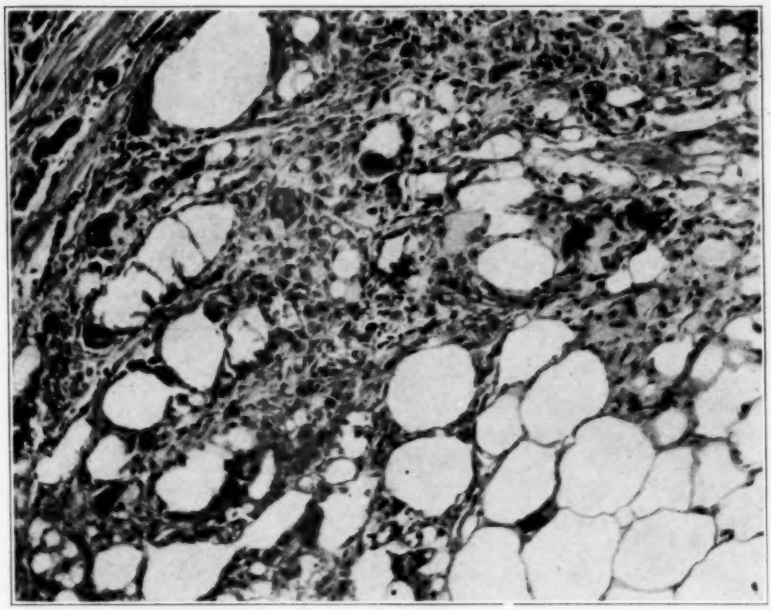

Fig. 4.—Photomicrograph (× 165) of moderately advanced fat necrosis. Note the connective tissue proliferation about the broken-down confluent fat. (The specimen was stained with eosin and methylene blue.)

Fig. 5.—Photomicrograph (× 900) showing the more abundant cellular reactions which may occur in fat necrosis. Here, in addition to mononuclear phagocytes, are numerous lymphocytes and plasma cells. In an earlier stage polymorphonuclear leukocytes may be seen. (The specimen was stained with eosin and methylene blue.)

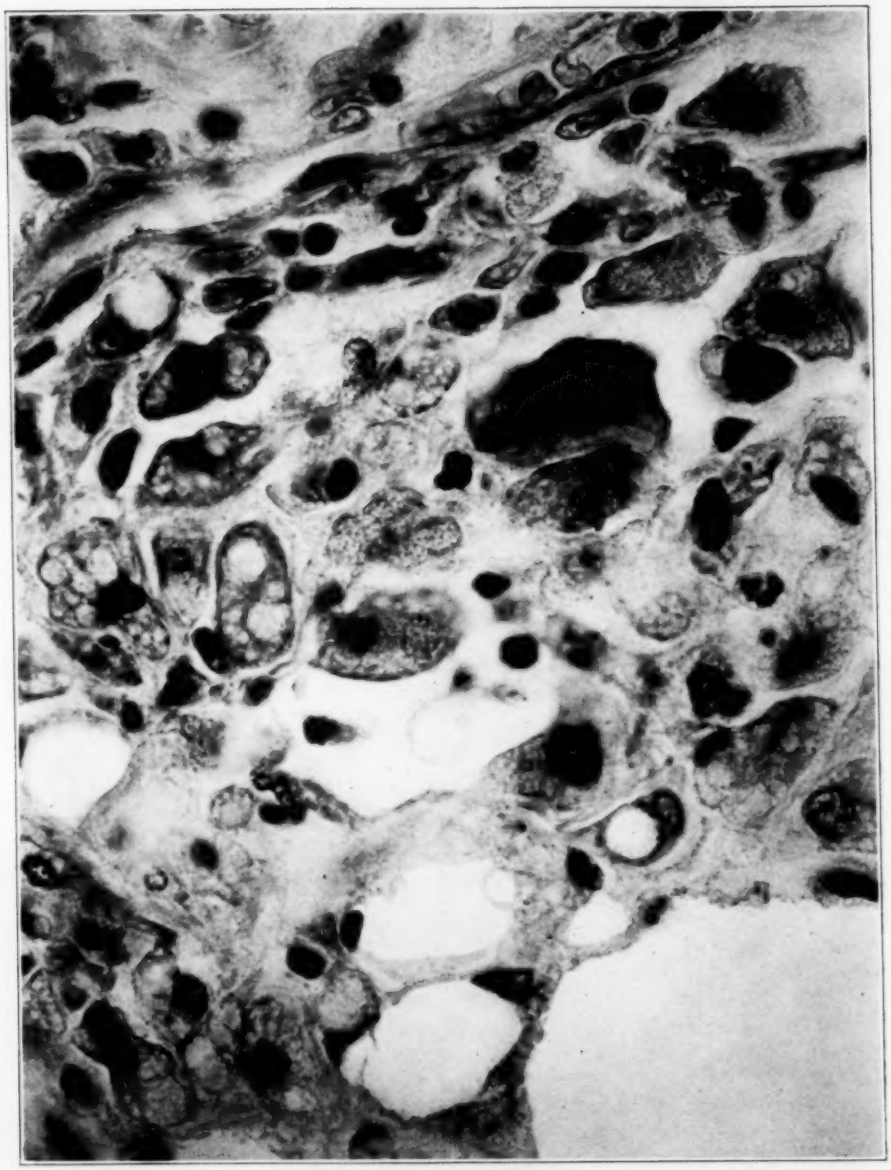

Fig. 6.—Photomicrograph (× 900) showing a marked foreign body reaction with the formation of giant cells in an area of fat necrosis. (Specimen was stained with eosin and methylene blue.)

connective tissue and to some extent of the fat cells (fig. 4). The cellular infiltration may be heavy, and in addition to the mononuclear phagocytes there may be numerous lymphocytes, plasma cells and occasional polymorphonuclear leukocytes (fig. 5). In early fat necrosis, a stage not often seen histologically, polymorphonuclear leukocytes may be numerous. In a later stage, giant cells frequently constitute a prominent feature (figs. 6 and 7), so that in some instances the lesion bears a superficial resemblance to tuberculosis. More commonly, however, as the lesion develops one finds many cystlike areas of necrotic fat, sur-

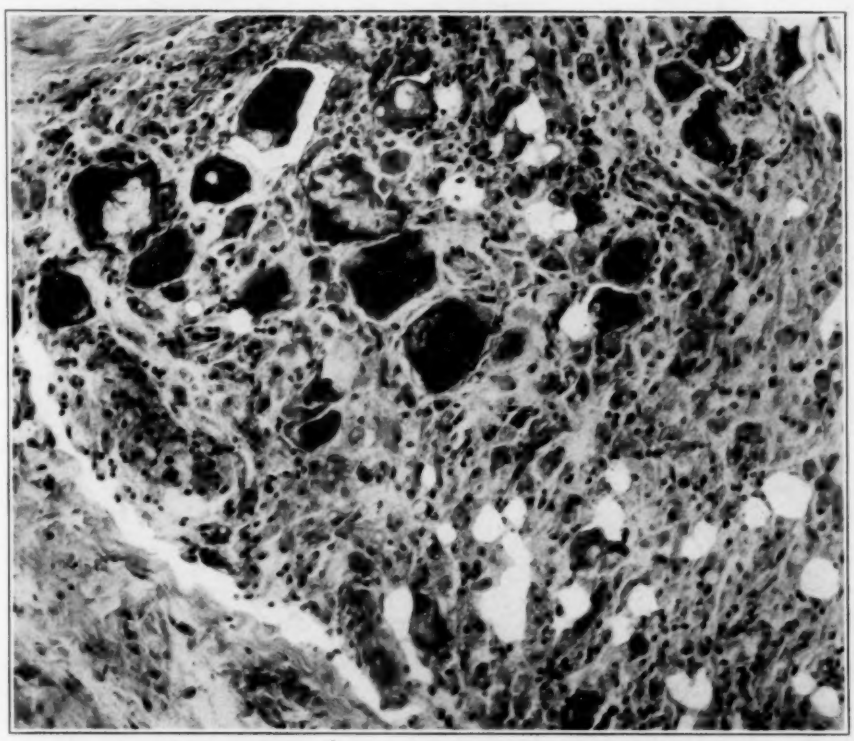

Fig. 7.—Photomicrograph (× 165) showing the formation of numerous giant cells in an area of fat necrosis. Histologically the lesion may bear a resemblance to tuberculosis. Note the fatty acid crystals within the giant cells. (The specimen was stained with eosin and methylene blue.)

rounded by mononuclear phagocytes and giant cells and separated by broad bands of proliferating connective tissue (fig. 8). These cystic areas may become macroscopically visible but rarely exceed 1 cm. in diameter.

Obliterative endarteritis is occasionally associated with fat necrosis, particularly in the late stages. In some cases such vascular changes

may constitute the causative factor. Usually, however, the obliteration of the vessels is an accompaniment of the contraction and hyalinization of the connective tissue, which occurs throughout the area of fat necrosis. In the very late stages the cellular reaction may completely subside, leaving only the cystlike areas, which are surrounded by dense, hyalin-

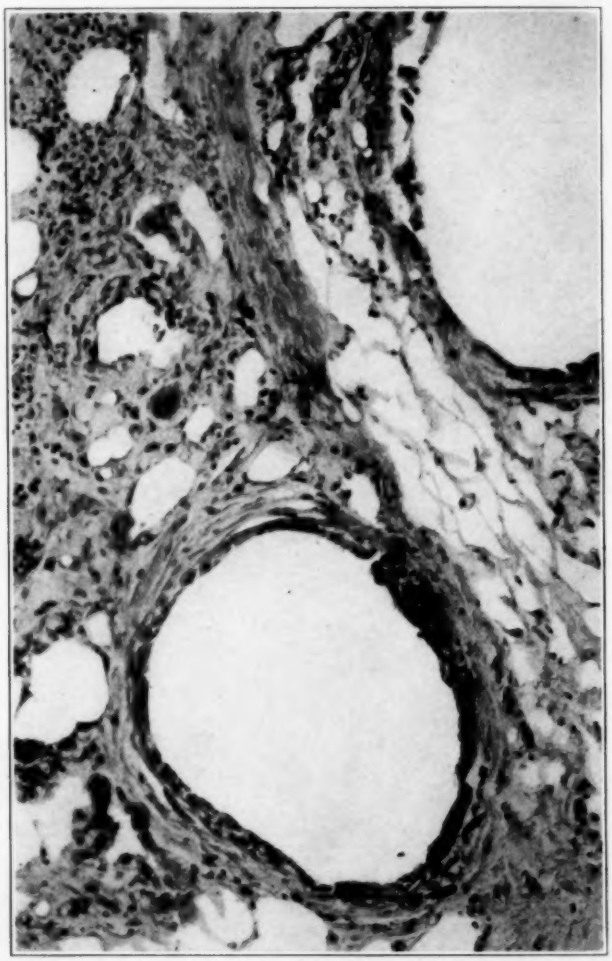

Fig. 8.—Photomicrograph (× 165) of advanced fat necrosis. Here one finds the confluent spaces of necrotic fat surrounded by a wall of phagocytes and giant cells and separated by broad bands of connective tissue. This is the characteristic histologic picture of fat necrosis. The pseudocysts become macroscopically visible but rarely exceed 1 cm. in diameter. (The specimen was stained with eosin and methylene blue.)

ized acellular scar tissue (fig. 9). In this stage areas of calcification are not uncommon.

The gross appearance of fat necrosis varies considerably, depending on the stage in which it is observed. Hadfield [7] stated that in the very early stages of fat necrosis the lesion may occupy exactly one or two fat lobules, appearing as a sharply demarcated, opaque area which stands out prominently against the normal fat surrounding it. It is soon followed by central liquefaction of the lesions, and then one finds

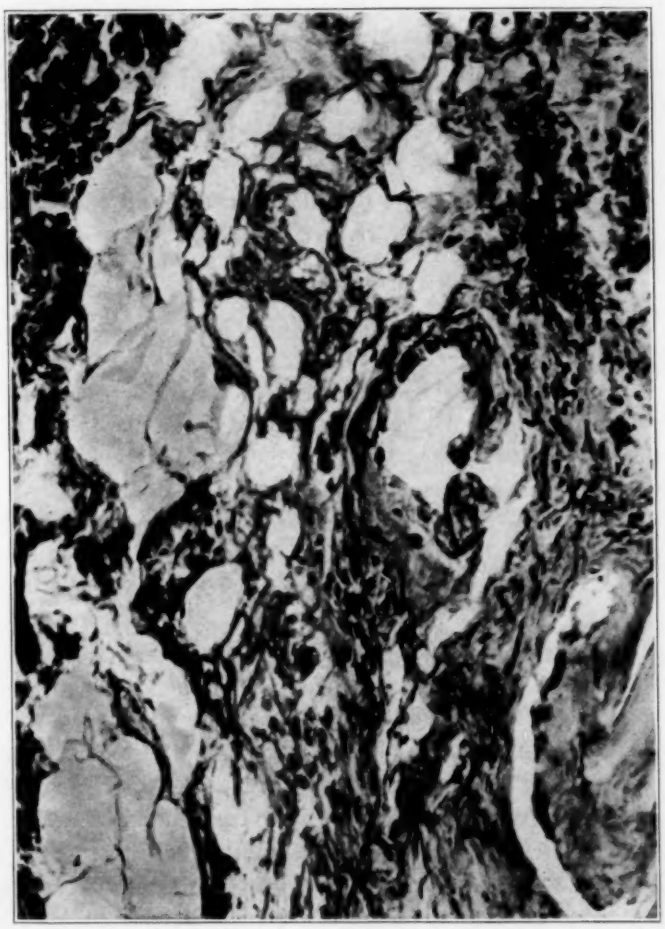

Fig. 9.—Photomicrograph of an area of late fat necrosis. The cellular reaction has subsided, and the connective tissue is undergoing hyalinization.

a poorly demarcated, edematous area of fat in which minute cystic spaces are visible and from which yellow, oily material may be expressed.

7. Hadfield, G.: Fat Necrosis of the Breast, Brit. J. Surg. **17**:673-682 (April) 1930.

Later the induration becomes more striking, and the cut surfaces of the lesion contain well defined cavities filled with serous fluid, oily, necrotic fat or a grayish white, chalklike débris. This stage is easily recognized by gross inspection and corresponds to the stage of organization and cyst formation described microscopically (fig. 8). However, as the amount of connective tissue increases a more homogeneous grayish white appearance develops. There is also a gritty consistency, so that the tissue resists the blade of a knife in a manner much like that of scirrhous carcinoma. Even in this stage it is not likely that the experienced observer would mistake fat necrosis for carcinoma, but to one not familiar with it or not suspecting it the condition may prove deceptive. It is possible to interpret areas of necrotic fat as tumor, and in 1 case in the present series the correct diagnosis was in doubt until a histologic examination was made. Consequently, a biopsy with histologic examination of the tissue should be performed for suspected malignant tumor in those areas in which fat necrosis usually is encountered.

CLINICAL MANIFESTSTIONS

The incidence of fat necrosis cannot be accurately estimated because the lesion in many cases is not recognized. A considerable number of such lesions are treated as carcinoma. Thus, Hadfield [7] in a review of 45 collected cases of fat necrosis of the breast found that a radical mastectomy had been performed in 12 per cent. In the files of clinical diagnoses in the Peter Bent Brigham Hospital only 2 cases of extra-abdominal fat necrosis were recorded during the period between 1923 and 1937. In the department of pathology the diagnosis was made 10 times during this period. A study of a number of lesions of fat which had been diagnosed as chronic infection revealed 6 additional cases. An analysis of these 16 cases is outlined in table 1.

Twelve of the patients were females, and 4 were males. The age incidence varied from 16 to 68, the average being 50. One patient was in the second decade of life, none in the third, 5 in the fourth, none in the fifth, 6 in the sixth and 4 in the seventh. There seemed to be no relation between occupation and the development of fat necrosis. All of the patients were white except 1, who was a Negro. Six were described as obese, 9 were well developed and well nourished and 1 was of a thin, asthenic habitus. In this patient (case 10) the lesion was secondary to chronic infection. As one would expect, those patients who have an abundant panniculus are more susceptible to fat necrosis. The duration of the lesion is of no striking diagnostic importance. In the present series the nodule had been known to be present for periods varying from ten days to five years before operation was performed. A history of some form of trauma was mentioned by only 6 of the 16 patients. Only 1 of the patients had syphilis. None had diabetes.

TABLE 1.—*Summary of Sixteen Cases of Fat Necrosis*

Case	Age	Race	Sex	Occupation	Habitus	History	Etiology	Clinical Diagnosis	Pathologic Diagnosis	Treatment	Result
1	52	W	F	Bookkeeper	Well de-	Lump in right breast first	None discovered	Carcinoma of	Fat necrosis	Radical mas-	No recurrence

TABLE 1.—*Summary of Sixteen Cases of Fat Necrosis*

Case	Age Race	Sex	Occupation	Habitus	History	Etiology	Clinical Diagnosis	Pathologic Diagnosis	Treatment	Result
1	52 W	F	Bookkeeper	Well developed	Lump in right breast first noticed 10 days before admission	None discovered	Carcinoma of breast	Fat necrosis	Radical mastectomy	No recurrence
2	64 W	F	Housewife	Obese	Radical mastectomy 9 months before for carcinoma; nodule in operative scar for 1 month	Trauma	Recurrent carcinoma	Fat necrosis	Excision	No recurrence
3	52 W	F	Housewife	Obese	Radical mastectomy for carcinoma 4 months previously; nodule in scar for 2 months	Trauma	Recurrent carcinoma	Fat necrosis	Excision	No recurrence
4	37 W	F	Housewife	Obese	Lump in right buttock first noticed 10 weeks before admission; no pain or tenderness	None discovered	Malignant tumor	Fat necrosis	Biopsy	No further progression of the lesion
5	68 W	F	Housewife	Well developed	Lump in breast of 7 weeks' duration; no pain or tenderness	None discovered	Carcinoma of breast	Fat necrosis	Radical mastectomy	No recurrence
6	16 W	F	Schoolgirl	Well developed	Blow in calf of leg 5 years previously; small nodule near site of trauma ever since	Trauma	Deferred	Fat necrosis	Excision	No recurrence
7	57 W	F	Housewife	Obese	Nodule near site of varicose ulcer for 3 years	Chronic infection and trauma	Varicose ulcer with localized abscess	Chronic inflammation in fat*	Excision	No recurrence
8	63 W	F	Housewife	Well developed	Nodule near site of varicose ulcer for 2 months	Chronic infection and trauma	Abscess in varicose ulcer	Chronic inflammation in fat*	Excision	No recurrence
9	35 W	F	Laundress	Obese	Nodule on palm of hand 3 months after burn	Trauma	Scar tissue	Chronic inflammation in fat*	Excision	No recurrence
10	33 W	F	Manicurist	Thin	Metastatic abscess of thigh, 2 months' duration	Infection	Abscess	Fat necrosis	Incision; drainage; biopsy	
11	36 N	M	Laborer	Obese	Lipoma of shoulder, 5 years' duration; frequently traumatized in lifting heavy objects	Trauma	Lipoma	Lipoma with fat necrosis	Excision	No recurrence
12	57 W	M	None	Well developed	Inguinal hernia incarcerated for 4 years	? Ischemia	Hernia	Fat necrosis in properitoneal fat	Repair of hernia with excision of nodule in properitoneal fat	
13	65 W	F	Housewife	Well developed	Nodule on abdomen for several months	None discovered	"Cyst"	Fat necrosis	Excision	No recurrence
14	32 W	M	Physician	Well developed	Fracture of leg 15 years before; trauma to site of fracture 8 weeks before admission	Trauma	"Nodule" in subcutaneous tissue	Fat necrosis	Excision	No recurrence
15	50 W	F	Housewife	Well developed	Lump beneath the angle of the left jaw	None discovered	Wen	Chronic infection in fat*	Excision	No recurrence
16	50 W	M	Gas fitter	Well developed	Femoral hernia incarcerated	? Ischemia	Hernia	Fat necrosis in omental fat	Excision	

* Original histologic diagnosis made in 1923. When the material was reviewed the histologic character of these lesions was found to be that of fat necrosis.

It is remarkable that in none of these cases was the possibility of fat necrosis considered before operation. In 6 a clinical diagnosis of carcinoma was made, and in 2 radical surgical operations without biopsy were done. It would appear that there is need to call attention once again to the varied clinical manifestations of extra-abdominal fat necrosis.

The present series is representative of the various locations in which fat necrosis may arise (table 2). Of these the breast assumes by far the greatest importance. In this location fat necrosis appears as a firm, often painless nodule which gradually or sporadically makes rapid increases in size. It may be situated in any quadrant of the breast. A definite history of trauma has been obtained in only 40 per cent of the reported cases. In more than 50 per cent the lesion has been adherent to the skin, and occasionally the typical "peau d'orange" appearance of cancer has been observed. In 10 per cent there has been retraction of the nipple, and in about the same proportion the lesion

TABLE 2.—*Location of Lesions*

Area Involved	Number of Cases
Breast	2
Postoperative mastectomy scar	2
Lipoma of shoulder	1
Hernial sac (inguinal)	2
Subcutaneous tissue of lower extremity	3
Subcutaneous tissue of lower extremity with varicose ulcer	2
Subcutaneous tissue of upper extremity	1
Subcutaneous tissue of abdominal wall	1
Buttock	1
Subcutaneous tissue of neck	1

has been adherent to the deep tissues of the chest wall. A clinical diagnosis of fat necrosis of the breast is occasionally possible, particularly if after trauma to the breast a mass has developed rapidly and no involvement of the axillary lymph nodes is found. More often, however, the lesion is much like carcinoma in appearance, and only unusual circumspection will prevent an error. This means that for even a "typical carcinoma" of the breast a biopsy must be performed and histologic examination by means of a frozen section must be made before radical surgical treatment is given. Case 1 illustrates the difficulty in diagnosis which fat necrosis may present.

CASE 1.—I. H., a woman aged 52, unmarried, a bookkeeper, was admitted to the hospital because of a lump in the breast, first noticed ten days prior to admission. There was no history of trauma, pain or tenderness in the nodule. There had been no discharge from the nipple. Physical examination disclosed a well preserved woman. In the outer half of the right breast, on a level with the nipple, there was a mass which measured 2 by 1.5 by 1.5 cm. It was firm and slightly irregular but freely movable. There was dimpling of the skin over the nodule. A few small, soft lymph glands were palpated in the axilla. Laboratory studies revealed nothing abnormal. A clinical diagnosis of carcinoma of the breast was made, and operation was advised. At operation an incision was made

into the tumor, and as the gross appearance of the tissue at the depth of the wound seemed characteristic of carcinoma a radical mastectomy was performed. Examination of the specimen after excision disclosed a mass of hard, firm tissue, measuring roughly 4 cm. in diameter, situated in the upper outer quadrant of the breast. Grossly, the lesion was suggestive of carcinoma. Histologic examination, however, revealed a large area of fat necrosis with extensive fibrous tissue reaction at the periphery. There was no evidence of neoplasm.

The development of fat necrosis in a mastectomy scar presents even greater difficulties in diagnosis, particularly if the mastectomy has been performed for carcinoma. There were 2 such cases in the present series, and it is likely that the condition is more common than has been realized. In this situation fat necrosis appears as a hard, irregular nodular growth which is usually fixed to the chest wall. Unless the possibility of fat necrosis is kept constantly in mind a diagnosis of recurrent carcinoma is inevitable. The following cases are examples.

CASE 2.—L. P., a woman aged 64, divorced, was admitted to the hospital because of a nodule in the operative scar of a radical mastectomy which had been performed for adenocarcinoma six months previously at another hospital. The patient was a moderately obese woman in good general health. The physical examination disclosed as the only abnormality a hard, fixed irregular nodule 3 by 1 by 1 cm., in the operative incision. This was fixed to the underlying tissues and was interpreted as a nodule of recurrent carcinoma. At operation this nodule was so widely excised that a plastic procedure was necesary to close the wound.

Gross inspection of a cut surface of the excised tissue revealed numerous small cysts filled with viscid, oily material. A diagnosis of fat necrosis was made, and this was confirmed by histologic examination.

CASE 3.—L. C., a Jewish woman aged 52, a housewife, was admitted to the hospital because of a lump in the left breast, of four weeks' duration. There had been no pain, tenderness or discharge from the nipple. Physical examination showed an obese woman. The breasts were pendulous. There was a hard, slightly irregular nodule in the lower inner quadrant of the left breast. This was freely movable. The axillary nodes were easily palpable and were stony hard. A radical mastectomy was performed for what proved to be adenocarcinoma. Skin grafting was necessary to close the wound. Postoperatively there was much bloody discharge from the wound. There was also considerable sloughing of the skin flaps. The wound healed slowly by secondary intention.

Four months after this operation the patient noticed a small nodule in the upper portion of the scar and came at once to the hospital. At this admission the physical examination showed the patient to be in good general health. There was a bean-sized, irregular, hard but freely movable nodule in the upper portion of the scar. The tissues adjacent to this nodule were firm. A diagnosis of recurrent carcinoma of the breast was made. At operation a rather extensive dissection of the scar tissue was done, and before a histologic diagnosis of fat necrosis was made the surgeon was planning to remove a portion of the chest wall. A frozen section prevented unnecessary surgical intervention, as it showed no evidence of carcinoma.

Such cases as these are an adequate indication for biopsy and histologic examination of the tissue before surgical intervention or irradiation is employed in the treatment of a lesion suspected to be recurrent carcinoma of the breast. It should be noted that fat necrosis may not develop for months or even years after trauma to the normal breast. Hence, in cases in which fat necrosis occurs in mastectomy scars the length of time after operation which elapses before the lesion develops may be variable.

Elsewhere in the body, fat necrosis is less likely to be mistaken for a malignant neoplasm, but it may prove a baffling lesion. The following case is an example.

CASE 4.—L. S., a Canadian-born woman aged 64, a housewife, was admitted to the hospital because of a painful tumor of the right buttock, first noticed ten weeks prior to admission. There was no history of unusual trauma. Since it was first noticed the tumor had not increased in size. The patient sought medical advice because of lancinating pain arising in the region of the growth and radiating down the thigh. Physical examination disclosed an irregular, poorly circumscribed, slightly tender mass just above and lateral to the right ischial tuberosity. The nodule was situated deep in the fatty tissues of the buttock and was firm but not hard. Except for obesity the examination showed no abnormal conditions. The results of laboratory studies were not remarkable. The Wassermann and Hinton tests gave negative results.

At operation a nonencapsulated, hard, gritty tumor was encountered. The cut surface of the lesion was whitish yellow, and the gross appearance suggested malignancy. A frozen section revealed fat necrosis and no evidence of tumor. A radical dissection of the lesion was thus prevented.

Other situations in which fat necrosis may occur are (1) an old incarcerated hernial sac (2) a lipoma and (3) any place where a nodular lesion develops after trauma or long-standing infection. In an old incarcerated hernial sac, either the omentum or the properitoneal fat is involved. This occurs independently of any lesion in the pancreas. Usually the condition manifests itself as a moderate induration of the fat and does not attract the attention of the operator, but in 1 case in the present series there was a solitary whitish gray, firm nodule fixed to the under surface of the hernial sac. It strongly suggested the seeding of an intra-abdominal tumor, and it might easily have led to an unnecessary exploration of the abdomen if its true nature had not been suspected and the diagnosis confirmed histologically. In a lipoma, areas of fat necrosis may impart an irregularly nodular consistency to the tumor, causing it to be mistaken for a sarcoma.

The development of carcinoma in areas of chronic inflammation is a fairly common clinical observation.[8] It is not generally known, however, that occasionally fat necrosis may arise in or adjacent to such areas. In the present series there were 3 instances of such origin, but in each case the small tumor mass which developed was interpreted

as an indurated abscess cavity rather than a neoplasm. However, in view of the similarity which fat necrosis bears to neoplasm elsewhere in the body it is not unlikely that in certain cases it may also simulate malignant disease in this situation.

SUMMARY

Attention is again called to the fact that fat necrosis in the breast or in the subcutaneous tissues may present the clinical aspects of a malignant neoplasm and thus lead to ill advised surgical treatment or irradiation therapy. The etiologic factors and the pathogenesis of this condition are discussed, and its varied clinical manifestations are described. The lesion may be encountered anywhere in the body, but it should be suspected particularly in the presence of pathologic change in the breasts and in mastectomy scars, because in these locations a mistaken diagnosis leads to unnecessarily radical surgical or irradiation therapy. The possibility of fat necrosis must be kept in mind, and biopsy with histologic examination of the tissues must be performed before operation or irradiation therapy is employed for a nonexistent malignant lesion.

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8. Harrison, J. H.: Epidermoid Carcinoma in Osteomyelitis: Case Report, Am. J. Cancer **32**:527-533 (April) 1938.

REPAIR OF HERNIA WITH PLANTARIS TENDON GRAFTS

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The plantaris tendon is a suitable structure for grafting and can be used in operations usually performed with grafts of fascia lata, over which it has several advantages. My object in this paper is first to state the relevant facts about the anatomy of the tendon, secondly to describe a method of removing it and thirdly to describe its use as a graft in the repair of hernia.

ANATOMY

The plantaris tendon is absent in 7.5 per cent of subjects, according to Gruber as quoted in Quain's "Anatomy" [1] (1892). In a further proportion of cases it is too slender to be used as a graft in hernia repair, although it may be adequate for other purposes as a suture material. In 100 consecutive postmortem examinations I found the tendon absent or inadequate in 16. This constitutes the sole disadvantage of the proposed use of the tendon. The deficiency, however, is more common in women than in men, and it is for the latter that the graft is mostly required for hernia repair. Moreover, the tendon is often palpable through the skin, and although its absence cannot be inferred when it is impalpable it is often possible to determine that it is present and well developed before an operation is begun.

The plantaris muscle arises from the lateral condyle of the femur, and its long tendon passes obliquely through the calf in the avascular plane between the gastrocnemius and the soleus muscle. This plane is readily opened by blunt dissection. The length of the fleshy part of the gastrocnemius is variable, and when it is short, as much as 6 inches (15 cm.) of the plantaris tendon may be lying subcutaneously on the achilles tendon. Its termination is variable, as also is its relation at the lower end to the achilles tendon. It may have a separate insertion into the calcaneus muscle beside the larger tendon or it may blend with it and share its insertion. In other cases it is inserted into the deep fascia of the leg or into the internal annular ligament. The latter

1. Quain, J.: Elements of Anatomy, ed. 10, edited by A. Schäfer and G. D. Thane, London, Longmans, Green & Co., 1892, vol. 2, pp. 264.

arrangements are usually found with very slender tendons. Quain stated that the plantaris tendon is sometimes enclosed in the lower part of the achilles tendon, but I have not met with this variety either at operation or at postmortem examination. When the two tendons blend to share a common insertion, the plantaris spreads at its lower end into a fan-shaped thin sheet which embraces the achilles tendon (fig. 1). This is one reason for making the incision to expose the lower end a little above the insertion. Through this incision the tendon will be found in one of three places. Usually it lies closely applied to the medial border of the achilles tendon; if not here it will probably be found in the fat on the medial side, sometimes as much as ½ inch (1.27 cm.) in front of the achilles tendon; rarely it is closely applied to its deep aspect.

The part of the tendon below its emergence from under the gastrocnemius muscle is crossed obliquely by several leashes of blood vessels which might be injured in the proposed method of extraction. There

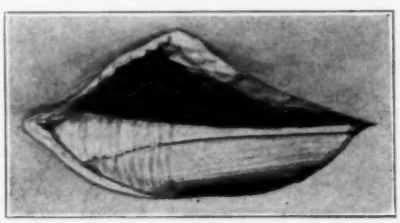

Fig. 1.—Right plantaris tendon exposed at lower end. The tendon lies flat on the achilles tendon, spreading out over its lower end into the shape of a fan.

has been no evidence of this accident in my experience. Sometimes after the extraction of the tendon a few muscle fibers are found adherent about its middle. These come from the soleus, and although easily stripped from the tendon they probably represent a functional attachment, since in such cases the tendon is larger in its lower than in its upper half, whereas the reverse is found when there is no such attachment.

Occasionally the soleus muscle has a small accessory tendon lying medial to and separate from the achilles tendon. This may be mistaken for the plantaris tendon through a small incision, but the mistake may be avoided by noting the greater tension in the short soleus tendon and the presence of muscle fibers entering it (fig. 2).

For the greater part of its course the tendon is lying in loose areolar tissue, allowing easy separation by blunt dissection, but where it passes under the edge of the gastrocnemius it may be held close between that muscle and the soleus tendon, and a little difficulty may be encountered in separating it from them.

The tendon has the curious property of lateral stretching without splitting. Even a slender specimen may be pulled out easily into a sheet 2 inches (5 cm.) wide (fig. 3). A part of this lateral stretching occurs at the expense of length, and if the stretched tendon is pulled in its length it resumes its cordlike form. Use is made of this property in the method of repair of hernia to be described.

METHOD OF EXTRACTING THE TENDON

The leg is held by an assistant, externally rotated so that its medial aspect is exposed. An incision 1 inch (2.5 cm.) long is made over the medial aspect of the achilles tendon a little above its lower end. One reason for thus placing the incision has already been given, i. e.,

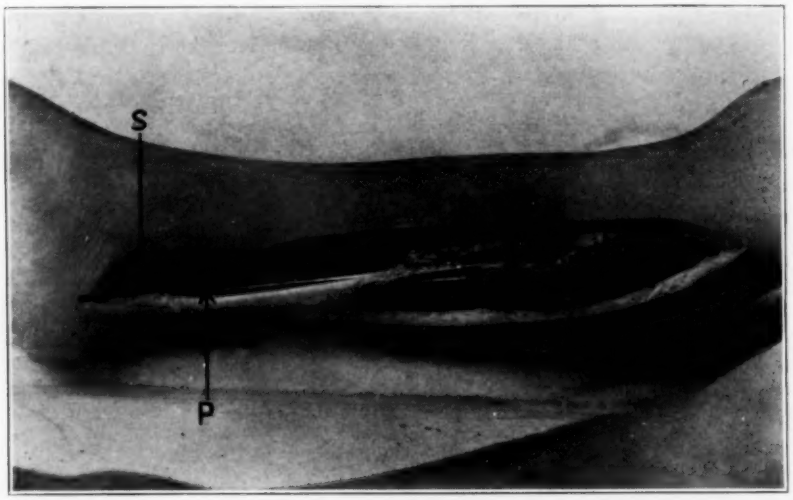

Fig. 2.—Accessory soleus tendon found post mortem. *S*, soleus tendon; *P*, plantaris tendon.

that the tendon spreads out into a fan at its insertion and may be difficult to identify. I have also thought it advisable to place the incision so that the scar shall not be subject to pressure from the edge of the shoe. If the tendon is in its most common place it will be exposed by the incision and will be seen lying on the achilles tendon (fig. 1). If not present here it should be sought in the fat anteromedial to the tendon, where it is easily identified if made taut by dorsiflexion of the foot. Finally, it may sometimes be found closely applied to the anterior aspect of the achilles tendon. When found it is cleaned in the length of the wound and divided as low as possible. The cut end is then passed through the eye of the stripper (fig. 4), which is the only special instrument required and is a modification

of Mayo's varicose vein enucleator (fig. 5). The eye of the stripper, threaded over the tendon, is then inserted in the wound and pushed up the leg while tension is maintained on the cut end. Very little resistance is encountered to the passage of the stripper, but it may require a little coaxing about the middle of the tendon, where it lies in the angle at the junction of the gastrocnemius and soleus tendons. The stripper is pushed up until the eye lies just below the popliteal fossa. A second incision, 1 inch (2.5 cm.) long, is now made over the

Fig. 3.—Plantaris tendon spread laterally (centimeter scale).

medial edge of the tibia near its upper end where it expands toward its head. This incision is carried through the deep fascia, which is a forward extension of that enclosing the gastrocnemius muscle. The incision in the deep fascia opens the plane between the gastrocnemius and the soleus muscle. The muscles are separated by blunt dissection and held apart with the blades of a large artery forceps (fig. 6*A*). The assistant by manipulating the handle of the stripper can direct its eye toward the surface of the wound, the tendon at this level being deep because of its oblique course toward the lateral condyle of the

femur. The tendon is easily identified in the eye of the stripper and is divided as high as possible (fig. 6*B*). Tendon and stripper are then withdrawn through the lower incision, and both incisions are closed. No vessels of any size need be divided by the incisions, the subcutaneous veins in the upper part being usually visible and easy to avoid. At first the upper incision was made on to the eye of the stripper while the assistant directed it to the surface, but this method was abandoned, as it was feared the saphenous nerve might be injured. Because of the possibility of bleeding from the leashes of vessels crossing the lower half of the tendon, a crepe bandage is applied to the leg.

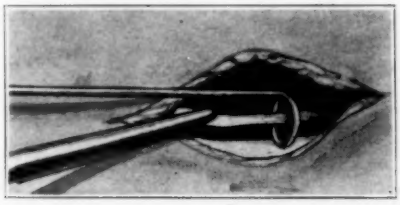

Fig. 4.—Plantaris tendon exposed at the lower end, divided and threaded through the eye of the stripper.

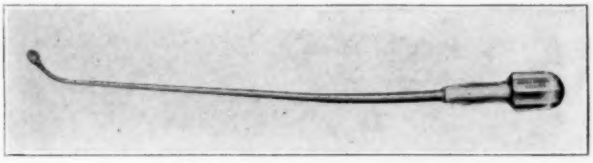

Fig. 5.—Tendon stripper.

METHOD OF HERNIA REPAIR

The tendon is used as a graft and not as a suture. The method of fascial suturing described by Gallie and Le Mesurier [2] in 1924 is open to the objection that the passage of the large needle through aponeurotic structures results in splits which may enlarge and become the openings for recurrent hernia. Recurrent inguinal hernia is usually direct, and tearing of the conjoined tendon after suture to the inguinal ligament probably plays a part in its causation. Apart from the passage of large needles, the risk of tearing also makes it essential to avoid tension, and although Gallie and Le Mesurier deprecated tension in the fascial sutures the approximation of conjoined tendon and inguinal ligament depicted in their paper can rarely be obtained without it. A further objection to their method is that it depends for success on the survival

2. Gallie, W. E., and LeMesurier, A. B.: Brit. J. Surg. **12**:289, 1924.

of the graft, and although their animal experiments suggested that this might be expected, experience with hernia operations shows that it is by no means certain. The validity of these objections is supported by published results of fascial suture. For example, Burdick and his associates [3] in 1937, reporting 1,485 operations, found a recurrence rate of 29.1 per cent. These authors pointed out that fascial suture was mostly used for difficult cases, but it was for these especially that the method was devised. In many of their cases of recurrence they found no trace of the fascial suture used at the first operation.

The method of repair with plantaris tendon is intended to overcome some of these objections. It is hoped that the tendon will be less readily absorbed than fascia lata, but as yet there is no evidence on

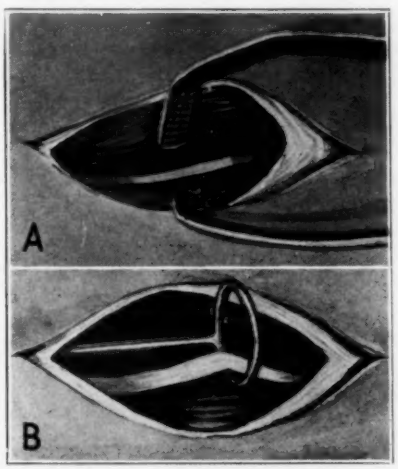

Fig. 6.—*A*, plantaris tendon exposed at the upper end, lying between the soleus and the gastrocnemius muscle. *B*, plantaris tendon directed to the surface of the upper wound with the eye of the stripper.

this point. On the assumption, however, that absorption may occur, the graft is fixed in position with unabsorbable sutures of thread or silk which, acting as foreign bodies, stimulate fibrous tissue which is permanent. Fibrosis stimulated by absorbable agents is not permanent, as can be seen in the treatment of hernia by injection.

After the usual treatment of the sac the inguinal canal is prepared for the graft. In the case of direct hernia the defect in the transversalis fascia is closed with silk or thread. The inguinal ligament and conjoined tendon are cleared of areolar tissue. The proportion of muscle and aponeurosis in the internal oblique and transversalis muscles varies,

3. Burdick, C. G.; Gillespie, D. H. M., and Higinbotham, N. L.: Ann. Surg. **106**:333, 1937.

as has recently been shown by Anson and McVay [4] (1938), and the details of grafting are adapted to suit the conditions found. As far as possible the graft is fixed to aponeurotic rather than muscular structures, and where the internal oblique is muscular it may be better to use the underlying transversalis aponeurosis. Rarely do the muscle

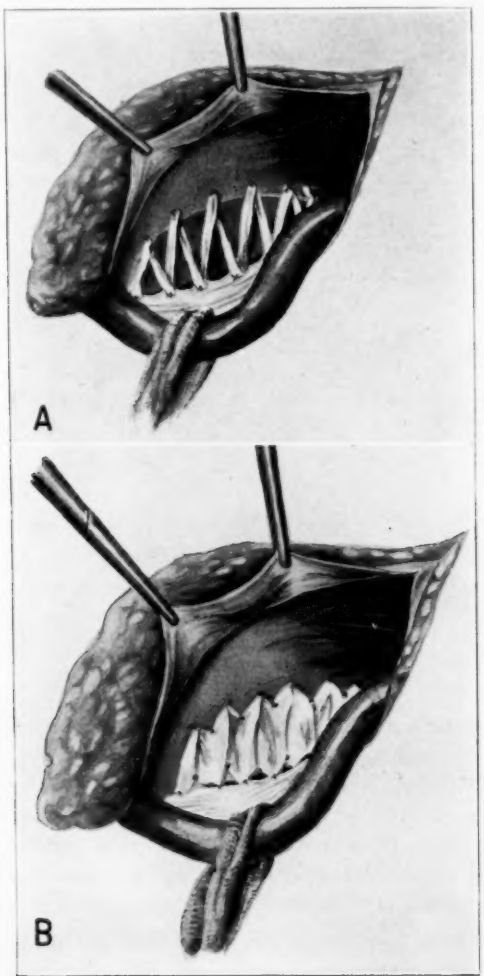

Fig. 7.—*A*, graft stitched in position before spreading of the strands. *B*, adjacent strands of graft spread and sutured to one another.

fibers of the transversalis extend as low as the spermatic cord. The graft is fixed in a zigzag pattern, being sutured alternately to the inguinal ligament and the conjoined tendon or one of its components with fine silk or thread (fig. 7*A*). Care must be taken that the

4. Anson, B. J., and McVay, C. B.: Surg., Gynec. & Obst. **66**:186, 1938.

medial angle is adequately covered. There is no tension on the graft, and no attempt is made to approximate the conjoined tendon to the inguinal ligament. The outer end of the graft may be fixed in a loop around the internal ring. After the graft has been fixed in the zigzag fashion, adjacent strands are sutured to one another, the property of lateral stretching allowing this to be done without tension (fig. 7*B*). In this way the grid of tendon strips is converted into the equivalent of a continuous fascial sheet. The cord is replaced and the wound closed in layers.

The advantages claimed for the method are as follows. The structure used as a graft is removed with very little trauma, and its removal causes no disability. Being tendinous the graft is probably less easily absorbed than fascia. The graft is inserted with minimal trauma to the structures between which it acts as a bridge. It is fixed without tension with unabsorbable sutures; this excites fibrosis which persists even if the graft is absorbed. Lateral stretching of the graft makes approximation of adjacent strands possible without tension.

SUMMARY

The plantaris tendon can be used for operations usually performed with fascia lata.

It lies in a plane that is mainly avascular and can be removed with little trauma through two small incisions over its ends.

It is sometimes absent or inadequate for its proposed use.

In hernia repair it is used as a graft and not as a suture to reenforce the posterior wall of the inguinal canal.

The graft should be fixed with unabsorbable sutures.

Its property of lateral stretching enables the gridlike arrangement of the graft to be converted into a continuous sheet.

SUBDURAL HEMATOMA

DIAGNOSIS AND TREATMENT

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AND

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BALTIMORE

In 1925 Cushing and Putnam [1] published reports of 11 cases of subdural hematoma in which the condition apparently arose as the result of trauma to the head. At the same time they summarized the theories regarding the nature of this lesion and discussed its relation to the pachymeningitis haemorrhagica interna described by Virchow.[2] They expressed the opinion that the only pathologic difference between the two is in the microscopic appearance of the membranes of the hematoma, the traumatic form possessing large mesothelial-lined spaces and smaller capillaries. They also concluded that late hemorrhages into the sac are of common occurrence. In 1927 Griswold and Jelsma,[3] in a similar study, concluded that the microscopic appearance of the membranes was the same in both forms. Whatever the relation between the two forms of subdural hematoma, these papers served to emphasize the importance of trauma as a cause, if not the only cause, of the lesion considered in this paper. Such causation is in contradistinction to that of Virchow's pachymeningitis, a condition which occurs in decrepit persons and probably results from systemic causes. Although the microscopic appearance of the membranes is essentially the same with the two types of lesion, the gross lesions are entirely different; with Virchow's pachymeningitis there is solid, thick membrane with little or no blood, and with subdural hematoma these membranes are very thin and the blood is in great volume. As early as 1804, Bell [4] in his "A System of Surgery" wrote of the importance of incising the dura after trephining the skull, for the possible release of subdural blood, in cases of head injuries in which an extradural hemorrhage is not encountered. (There is no record of a case in which the lesion was

1. Putnam, T. J., and Cushing, H.: Chronic Subdural Hematoma, Arch. Surg. **11**:329 (Sept.) 1925.

2. Virchow, R.: Hematoma durae matris, Verhandl. d. phys.-med. Gesellsch. **7**:134, 1857.

3. Griswold, R. A., and Jelsma, F.: Chronic Subdural Hematoma, Arch. Surg. **15**:45 (July) 1927.

4. Bell, B.: A System of Surgery, ed. 3, Philadelphia, T. Dobson, 1806, vol. 2, chap. 10.

cured in this way by Bell.) He further stated that subdural hemorrhages may not give rise to symptoms for several weeks after the injury. The frequency with which cases of traumatic subdural hematoma were reported in surgical papers during the nineteenth century is indicated by the article of Bowen,[5] who in 1905 was able to collect 72 cases (presenting both acute and chronic conditions) from the literature. He divided them into two groups. In the first were those in which the hematomas were unassociated with severe cerebral injury, the hemorrhages apparently having arisen from a tear in a pial vein or a vein running to the longitudinal sinus, and in the second group were those in which the hematomas were associated with severe cerebral lacerations or contusions and produced immediate symptoms. He pointed out that in the first group a period of freedom from symptoms after the injury frequently occurred. Henschen[6] in 1912 also reviewed a series of cases in which the condition was of traumatic origin, and Trotter[7] in 1914 called attention to the fact that the causative injury may be trivial. Subsequently, Rand[8] in 1926 demonstrated that the pial vessels were the source of the hemorrhage in several of his cases. The traumatic origin of this lesion is now widely accepted, as is indicated by the recent papers of Kaplan,[9] Fleming and Jones,[10] McKenzie,[11] Gardner,[12] Fischer and de Morsier,[13] Keegan,[14] Frazier,[15] Coleman,[16] and Furlow.[17] A full discussion of its occurrence in infants is given in a paper of

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5. Bowen, W. H.: Traumatic Subdural Hematomas, Guy's Hosp. Rep. **59**:21, 1905.

6. Henschen, K.: Diganostik und Operation der traumatischen Subduralblutung, Arch. f. klin. Chir. **99**:67, 1912.

7. Trotter, W.: Chronic Subdural Hemorrhage of Traumatic Origin and Its Relation to Pachymeningitis Hemorrhagica Interna, Brit. J. Surg. **2**:271, 1914.

8. Rand, C. W.: Chronic Subdural Hematoma, Arch. Surg. **14**:1136 (June) 1927.

9. Kaplan, A.: Chronic Subdural Hematoma, Brain **54**:430, 1931.

10. Fleming, H. W., and Jones, O. W., Jr.: Chronic Subdural Hematoma, Surg., Gynec. & Obst. **54**:81, 1932.

11. McKenzie, K. G.: Surgical and Clinical Study of Nine Cases of Chronic Subdural Hematoma, Canad. M. A. J. **26**:534, 1932.

12. Gardner, W. J.: Traumatic Subdural Hematoma with Particular Reference to the Latent Interval, Arch. Neurol. & Psychiat. **27**:847 (April) 1932.

13. Fischer, R., and de Morsier, G.: Chronic Subdural Hematoma Following Cranial Trauma, Presse méd. **41**:1517, 1933.

14. Keegan, J. J.: Chronic Subdural Hematoma, Arch. Surg. **27**:629 (Oct.) 1933.

15. Frazier, C. H.: Surgical Management of Chronic Subdural Hematoma, Ann. Surg. **101**:671, 1935.

16. Coleman, C. C.: Chronic Subdural Hematoma, Am. J. Surg. **28**:341, 1935.

17. Furlow, L. T.: Chronic Subdural Hematoma, Arch. Surg. **32**:688 (April) 1936.

TABLE 1.—*Summary Report of Forty-Eight Cases of Subdural*

Patient and Date of Admission	Age, Sex, Race	Chief Symptoms	Type of Trauma Time Before Admission	Duration of Symptoms	Latent Interval	Headache	Nausea or Vomiting	Drowsiness	Diplopia	Vertigo	Convulsions	Coma	Mental Confusion	Papilledema Retinal Hemorrhages	Involvement of Other Cranial Nerves	Motor and Sensory Changes	Reflex Changes	Ter
1 C. C. 2/28/14	26 M W	Headache; vertigo; failing vision; failing hearing; tinnitus	No history of trauma	14 mo.	0	+	+	0	0	+	0	0	0	Bilateral 5 to 6 D; nearly blind	Hearing impaired both ears	0	ep reflexes peractive both ies	T 98 P 60 WBC
2 G. B. 4/22/16	38 M W	Headache	Fall; unconscious; 8 weeks	8 wk.	0	+	+	+	0	0	0	0	0	Bilateral 6 D with hemorrhages	0	0	ep reflexes ore active left	T 98 P 60
3 L. D. 10/22/16	55 M W	Headache; drowsiness	Auto accident; not unconscious; 7 weeks	6 wk.	1 wk.	+	+	+	0	+	0	0	0	Bilateral 3 D	0	0	ep reflexes ore active left; binski sign left	T 10 P 60 BP 1 WBC
4 T. V. 12/11/16	24 M W	Headache; drowsiness; earache	Fall with unconsciousness; 4 weeks	4 wk.	0	+	0	0	0	0	0	0	0	Bilateral 2 D	0	0	ep reflexes peractive	T 98. P 66 BP 1
5 B. C. 12/27/16	47 M W	Headache; vomiting	Kicked on head by horse; unconsciousness; 3 years ?	2 yr.?	1 yr.?	+	+	0	0	0	0	0	0	Bilateral	0	0	ep reflexes ore active left	BP 1 WBC
6 J. T. 9/13/20	18 M W	Headache; vomiting	No history of trauma	10 wk.	0	+	+	0	0	+	0	0	0	Bilateral	0	Slight weakness of right side	ep reflexes ore active left; binski sign right	T 98. P 90
7 I. H. 12/19/22	26 M W	Headaches; drowsiness	Struck on left side of head boxing; 6 months	6 mo.	0	+	0	+	0	0	0	0	0	0	0	0	binski n on left	T 98. P 60 BP 9 WBC
8 L. B. 6/19/23	44 M W	Headache; drowsiness; paralysis right side	Struck head on auto fender; 3 weeks	2 wk.	1 wk.	+	0	+	0	+	0	+ 24 hr.	0	Bilateral papilledema	0	Flaccid paralysis right arm and leg	ep reflexes ore active right; binski sign right	T 100 P 70 WBC
9 D. L. 5/5/34	9 mo. F W	Enlargement of head; convulsions	Birth injury ?	5 mo.	0	0	0	0	0	0	+	0	0	0	0	Slight weakness left arm and leg	0	T 98.
10 W. S. 2/15/25	64 M W	Headache; mental confusion; drowsiness	Struck by auto; dazed; 8 weeks	8 wk.	0	+	+	+	+	+	0	+	+	0	0	0	mberg n	T 98. P 58
11 V. C. 5/27/25	30 M W	Headache; drowsiness	Struck by "knucks"; unconscious; 5 weeks	5 wk.	0	+	+	+	0	0	0	+	0	Bilateral	0	0	0	T 99. P 60
12 T. G. 7/7/25	40 M N	Headache; weakness of legs	Struck by auto; unconscious; 9 weeks	3 wk.	6 wk.	+	0	0	0	0	0	0	0	0	0	Marked muscular weakness, unable to walk	ateral binski n	T 98. P 60 BP 1
13 L. B. 11/13/25	37 M W	Headache; drowsiness	Struck head in fall; 6 months	6 mo.	0	+	+	+	0	+	0	+	+	Bilateral 1 D	0	0	0	T 98. P 46
14 L. S. 11/21/25	47 M W	Headache; weakness right side; unable to talk	Struck head in fall; unconscious; 5 weeks	4 wk.	1 wk.	+	0	+	0	0	0	0	0	0	0	Spastic paralysis right arm and leg; unable to talk	p reflexes re active right; binski positive on right e; stiff neck	T 98. P 80 WBC
15 J. A. 3/30/26	53 M W	Headache; drowsiness	0	8 wk.	0	+	+	+	+	+	0	0	+	Bilateral papilledema	0	Marked muscular weakness, unable to stand or walk	ateral binski n	T 99 P 46 BP 1 WBC
16 J. S. 7/10/26	43 M W	Headache	0	6 mo.	0	+	+	+	+	0	0	0	0	0	0	0	ateral binski n	T 98. P 56 BP 1
17 J. H. 8/31/26	32 M W	Drowsiness	Auto accident; unconscious 10 hours; 9 weeks	4 wk.	5 wk.	+	+	+	0	0	0	0	0	Bilateral papilledema	0	Left facial weakness (central)	p reflexes e active left	T 98. P 60 BP 1

Reflex Changes	Temperature, Pulse, Blood Pressure, W.B.C.	Other Positive Findings	Roentgen Findings	Clinical Impression	Trephine Ventriculography	Side of Lesion Type of Operation and Date	Recurrence After Operation	Result	Comment
eep reflexes peractive both des	T 98.6 F. P 60 WBC 6,400	Bulging right subtemporal decompression; operated on elsewhere 4 months previously	Erosion posterior clinoids	Tumor of the brain	0	Right craniotomy Mar. 14, 1914; drains used	0	Discharged well Apr. 9, 1914	Died one year later; cause unknown
eep reflexes ore active left	T 98 F. P 60	0	Normal	Tumor of the brain	0	Right subtemporal decompression; drains used; Apr. 23, 1916	0	Discharged well May 16, 1916	Well in 1937
eep reflexes ore active left; binski sign left	T 101.8 F. P 60 BP 130/80 WBC 15,000	0	0	Tumor of the brain	0	Right subtemporal decompression; drains used; Oct. 22, 1916	0	Discharged well Nov. 23, 1916	Died in 1932 of cardiac disease
eep reflexes peractive	T 98.6 F. P 66 BP 100/70	0	Fracture at base	None given	0	Right subtemporal decompression; drains used; Dec. 16, 1916	0	Discharged well Dec. 30, 1916	0
eep reflexes ore active left	BP 145/105 WBC 8,400	0	Normal	Tumor of the brain	0	Right craniotomy; drains; Dec. 27, 1916	0	Discharged well Jan. 11, 1917	History confusing as to when present illness began; well in 1937
eep reflexes ore active left; binski sign right	T 98.6 F. P 90	0	0	Tumor of the brain	+	Right craniotomy; drains; Sept. 20, 1920	0	Discharged well Oct. 8, 1920	Homolateral signs; well in 1937
binski gn on left	T 98.6 F. P 60 BP 95/50 WBC 11,200	Head is described as being very large	0	Tumor of the brain	+ Dec. 22, 1922	Left craniotomy; drains; Dec. 26, 1922	+ Subdural clot evacuated Dec. 26, 1922	Discharged well Jan. 13, 1923	Homolateral signs
eep reflexes ore active right; binski sign right	T 103.6 F. P 70 WBC 15,000	0	0	Cerebral tumor	0	Left craniotomy; drains; June 20, 1923	0	Died June 21, 1923	Autopsy showed no recurrence of hematoma; brain edematous
0	T 98.6 F.	Enlargement of head; right side larger than left; separation sutures	Hydrocephalus	Hydrocephalus	+	Right tap subdural space; 80 cc. obtained; May 6. 1924	0	Discharged well June 4, 1924	Well in 1933
mberg gn	T 98.6 F. P 58	0	0	Brain abscess or cerebral tumor	Trephine revealed hematoma, frontal	Right subtemporal decompression; drains; Feb. 15, 1925	Right craniotomy Feb. 25, 1925; removal bone flap Feb. 27, 1925	Discharged well Apr. 4, 1925	Subtemporal decompression insufficient for complete evacuation
0	T 99.2 F. P 60	0	0	Subdural hematoma	Trephine revealed hematoma	Left craniotomy May 27, 1925	+ Evacuation extradural hematoma May 29, 1925	Discharged well June 22, 1925	Well in 1937 save for focal epilepsy
lateral binski gn	T 98.6 F. P 60 BP 170/100	0	Normal	Tumor of the brain	+	Left craniotomy July 30, 1925	0	Discharged well Aug. 7, 1925	
0	T 98.6 F. P 46	0	Normal	Subdural hematoma	+	Left craniotomy, Nov. 13, 1926 120 cc. old blood	0	Discharged well Nov. 26, 1925	Well in 1937
eep reflexes ore active right; binski positive on right ck: stiff neck	T 98.6 F. P 80 WBC 20,000	0	Normal	Brain abscess	Trephine revealed hematoma frontal	Left craniotomy Nov. 25, 1925	Explored Dec. 1, 1925; extra- and subdural clots	Discharged well Feb. 2 1926	Well in 1937
lateral binski gn	T 99 F. P 46 BP 105/80 WBC 15,000	0	Normal	Tumor of the brain	+	Left craniotomy Mar. 21, 1926	0	Discharged well Apr. 15, 1926	Patient epileptic before hematoma; no convulsions during present illness; well in 1937
lateral binski gn	T 98.6 F. P 56 BP 117/70	0	Normal	Tumor of the brain	Trephine disclosed hematoma frontal	Left craniotomy July 12, 1926	Evacuation extra- and subdural hemorrhage July 13, 1926	Discharged well July 26, 1926	Well in 1937
ep reflexes re active left	T 98.6 F. P 60 BP 106/70	0	0	Subdural hematoma	Trephine disclosed hematoma	Bilateral craniotomy Sept. 15, 1926	0	Discharged well Oct. 29, 1926	Bilateral hematoma

Patient and Date of Admission	Age, Sex, Race	Chief Symptoms	Type of Trauma Time Before Admission	Duration of Symptoms	Latent Interval	Headache	Nausea or Vomiting	Drowsiness	Diplopia	Vertigo	Convulsions	Coma	Mental Confusion	Papilledema Retinal Hemorrhages	Involvement of Other Cranial Nerves	Motor and Sensory Changes	Reflex Changes	Temperature Pulse Blood Pressure W.B.C.
18 W. W. 11/15/26	57 M W	Headache; drowsiness	0	4 mo.	0	+	+	+	+	0	0	+ 12 hr.	0	0	0	0	o reflexes e active eft; eral inski sign	T 99.8 F. P 52 BP 120/ WBC 9
19 F. W. 12/27/26	20 M W	Headache	Struck on head in football game; 3 months	3 mo.	0	+	+	0	+	0	0	0	0	Bilateral 2 D	0	0	0	T 99 F. P 60 BP 110/ WBC 5
20 J. E. 11/24/27	59 M W	Headache; vomiting	0	4 mo.	0	+	+	0	0	+	0	0	+	0	0	0	0	T 98.6 F. P 58 BP 105/ WBC 1
21 F. F. 5/18/28	43 M W	Headache; drowsiness	0	6 wk.	0	+	0	+	0	0	0	Periods of coma	0	Bilateral less than 1 D	Left ptosis (iii)	Left facial weakness (central)	o reflexes e active eft	T 98.6 F. P 60 BP 180/
22 C. A. 11/28/28	26 M W	Headache; vomiting	Struck on head with bare fists; 8 weeks	5 wk.	3 wk.	+	+	0	0	+	0	0	0	Bilateral 1 D	0	0	0	T 98.6 F. P 62 BP 100/ WBC 8,
23 C. B. 3/15/29	52 M N	Headache; vertigo	0	5 wk.	0	+	0	0	0	+	0	0	0	Bilateral with hemorrhages	0	0	0	T 98.6 F. P 60 BP 115/ WBC 5,
24 J. O. 3/16/29	29 M W	Headache; loss of vision	Auto accident; unconscious; 1 year	1 yr.	0	+	0	+	+	+	0	0	0	Optic atrophy; blind	Anisocoria; right pupil larger than left	0	0	T 98.6 F. P 74 BP 90/6
25 W. W. 4/16/29	24 M N	Headache; vomiting	Punched about head in boxing; 6 weeks	6 wk.	0	+	+	0	0	0	0	0	0	Bilateral 1 D	0	0	0	T 98.2 F. P 58 BP 115/ WBC 7,
26 R. G. 9/24/29	18 M W	Headache; diplopia	0	3 wk.	0	+	+	0	+	+	0	0	0	Bilateral 1 D	Right facial (vii); absent corneal, left; motor V left; nystagmus	0	0	T 99 F. P 100 BP 120/ WBC 6,
27 F. P. 12/20/29	61 M W	Headache; vomiting	0	4 wk.	0	+	+	+	0	0	0	0	0	0	Nystagmus	0	0	T 97 F. P 66 BP 190/
28 W. M. 6/11/30	70 M W	Weakness and numbness of left extremity	0	6 mo.	0	0	0	+	0	0	0	0	0	0	0	Motor weakness of entire left side	reflexes active t; ski positive left	T 98.6 F P 60 BP 140/ WBC 7,
29 L. F. 6/11/30	38 F W	Headache; vomiting; tinnitus	0	6 mo.	0	+	+	0	+	0	Right focal	0	0	Bilateral 1 D; hemorrhages	0	Slight weakness right arm	reflexes active ght	T 98.6 F. P 90 BP 100/6 WBC 7,4
30 M. R. 5/15/31	53 F W	Headache; vomiting; drowsiness	Struck head during paroxysm of sneezing; 3 weeks	2 wk.	1 wk.	+	+	+	+	0	0	0	0	0	Bilateral ptosis; inability to look up; sluggish pupils (iii)	0	reflexes active; ral ski	T 99 F. P 60 BP 140/9
31 H. P. 6/15/31	53 M W	Headache	Struck by auto; unconscious; 4 months	4 mo.	0	+	0	+	0	0	0	0	0	0	0	Hypesthe left extre ities; par entire left side	reflexes active t side; ral ski	T 99 F. P 60 BP 98/62 WBC 7,9
32 S. H. 7/18/31	19 M W	Headache; staggering	0	8 mo.	0	+	+	0	0	+	0	0	+	Bilateral 2 D	0	General muscular weakness		T 99.6 F. P 62 BP 90/50 WBC 8,0
33 J. W. 1/23/32	67 M N	Headache; drowsiness	Struck head in fall; unconscious; 5 weeks	5 wk.	0	+	0	+	0	0	0	0	0	0	0	General muscular weakness	reflexes active; ral ski	T 100 F. P 60 WBC 10,
34 E. H. 6/28/32	51 M W	Headache; fainting spells	Struck head in fall; unconscious; 3 months	3 mo.	0	+	0	0	+	+	Focal right extremity	0	0	Bilateral 3 D; hemorrhages	Nystagmus; right pupil larger than left	0		T 99.6 F. P 80 WBC 6,0

Reflex Changes	Temperature, Pulse, Blood Pressure, W.B.C.	Other Positive Findings	Roentgen Findings	Clinical Impression	Trephine Ventriculography	Side of Lesion Type of Operation and Date	Recurrence After Operation	Result	Comment
...o reflexes ...e active ...eft; ...eral ...inski sign	T 99.8 F. P 52 BP 120/75 WBC 9,000	Arterio-sclerosis of peripheral vessels	Normal	Tumor of the brain	+	Right craniotomy Nov. 16, 1926	Nov. 18 evacuation extradural hemorrhage; Nov. 19 decompression	Discharged well Jan. 11, 1927	Small; removed intact with membrane
0	T 99 F. P 60 BP 110/60 WBC 5,400	0	0	Tumor of the brain	+	Left craniotomy Dec. 28, 1926	0	Discharged well Jan. 11, 1927	Well in 1937
0	T 98.6 F. P 58 BP 105/70 WBC 16,000	Arterio-sclerosis of peripheral vessels	0	Tumor of the brain	+	Right craniotomy Nov. 26, 1927	Evacuation extra- and subdural hemorrhage Nov. 29, 1927; same Dec. 2 1927	Discharged well Dec. 14, 1927	Well in 1937
...o reflexes ...e active ...ft	T 98.6 F. P 60 BP 180/1...	Arterio-sclerosis of peripheral vessels	Normal	Tumor of the brain	Trephine disclosed hematoma	Left craniotomy May 21, 1928	0	Discharged well June 14, 1928	
0	T 98.6 ... P 62 BP 100/60 WBC 8,400	0	Normal	Tumor of the brain	+	Right craniotomy Nov. 30, 1928	Evacuation extra- and subdural hemorrhage Dec. 2, 1928	Discharged well Dec. 22, 1928	
0	T 98.6 F. P 60 BP 115/70 WBC 5,300	0	Normal	Tumor of the brain	+	Left craniotomy Mar. 19, 1928	Evacuation extra- and subdural hemorrhage Mar. 21, 1929	Discharged well Apr. 1, 1929	Well in 1937
0	T 98.6 F. P 74 BP 90/60	0	0	Pituitary tumor	+ Cisternal air injection	Left craniotomy Mar. 24, 1929 (hematoma about sella)	0	Discharged improved Apr. 10, 1929	
0	T 98.2 F. P 58 BP 115/70 WBC 7,300	0	0	Subdural hematoma	Trephine disclosed hemorrhage, occipital	Left subtemporal decompression Apr. 19, 1929	0	Discharged well May 15, 1929	
0	T 99 F. P 100 BP 120/80 WBC 6,800	0	Normal	Tumor of the brain	+	Left craniotomy Sept. 25, 1929	0	Discharged well Oct. 7, 1929	5,000,000 R.B.C. bloody cerebrospinal fluid; hydroma associated with hematoma; well in 1937
0	T 97 F. P 66 BP 190/100	0	Normal	Tumor of the brain	+	Left craniotomy Dec. 20, 1929	Evacuation extra- and subdural hemorrhage Dec. 21, 1929; also twice more with removal bone flap	Discharged well Jan. 24, 1930	Died in 1935 angina pectoris
...reflexes ...active ...t; ...nski positive left	T 98.6 F. P 60 BP 140/100 WBC 7,300	Arterio-sclerosis of peripheral vessels	0	Cerebral hemorrhage	+	Right craniotomy June 14, 1930	Exploration; evacuation bloody fluid June 17	Died June 25, 1930; staphylococcus wound infection; meningitis	Autopsy; no abnormality noted save meningitis and membrane of hematoma; no recurrence
...reflexes ...active ...ght	T 98.6 F. P 90 BP 100/65 WBC 7,400	0	Normal	Tumor of the brain	+	Left craniotomy June 1930	0	Discharged well June 28, 1930	
...reflexes ...active; ...ral ...nski	T 99 F. P 60 BP 140/90	0	Normal	Tumor of the brain	+	Left craniotomy May 16, 1931	Evacuation extra- and subdural hemorrhage May 17; same and removal bone flap May 19	Discharged well June 4, 1930	Bleeding and clotting time normal; well in 1937
...reflexes ...active ...t side; ...ral ...nski	T 99 F. P 60 BP 98/62 WBC 7,900	Tenderness right frontal region	0	Subdural hematoma	0	Right craniotomy June 15, 1931	0	Discharged well June 30, 1931	Well in 1937
	T 99.6 F. P 62 BP 90/50 WBC 8,000	0	Normal	Tumor of the brain	+	Right craniotomy July 21, 1931	0	Discharged well Aug. 4, 1931	Well in 1937
...reflexes ...active; ...ral ...nski	T 100 F. P 60 WBC 10,400	Arterio-sclerosis of peripheral vessels	Normal	Cerebral hemorrhage	+	Left craniotomy Jan. 26, 26, 1932	0	Discharged well Feb. 2, 1932	Died 3½ years later of intestinal obstruction; no autopsy on head
	T 99.6 F. P 80 WBC 6,000	0	0	Subdural hematoma	0	Left craniotomy June 29, 29, 1932	0	Discharged well July 6, 1932	Well in 1937

TABLE 1.—*Summary Report of Forty-E[illegible]ses of Subdural*

Patient and Date of Admission	Age, Sex, Race	Chief Symptoms	Type of Trauma Time Before Admission	Duration of Symptoms	Latent Interval	Headache	Nausea or Vomiting	Drowsiness	Diplopia	Vertigo	Convulsions	Coma	Mental Confusion	Papilledema Retinal Hemorrhages	Involvement of Other Cranial Nerves	Motor and Sensory Changes	Reflex Changes	Temperature Pulse Blood Pressure W.B.
35 J. D. 7/25/32	65 M W	Headache; unconscious spells	Fall from a horse; unconscious; 3 months	3 mo.	0	+	+	+	0	+	+	0	+	0	0	0	[illegible]binski [illegible]n on [illegible]t	T 99.2 F. P 50 BP 90/[illegible]
36 J. H. 8/13/32	59 M W	Unconsciousness	Struck head in fall; unconscious; 1 week	1 wk.	0	+	0	+	0	0	0	+ 12 hr.	0	0	0	Deep re[illegible] bilater[illegible] hyperac[illegible]	[illegible]binski on right; [illegible]le clonus right	T 100.6 P 80 BP 150/[illegible]
37 P. F. 5/1/33	36 M W	Headache; drowsiness; tinnitus	In auto accident; unconscious; 6 weeks	6 wk.	0	+	+	+	0	0	0	0	0	Bilateral 2 D; hemorrhages	Absent corneal reflex left (v)	Hpyest[illegible] all ext[illegible]ities; l[illegible]terally; sense o[illegible]rical tion of[illegible]dity bilater[illegible]	p reflexes [illegible]eractive [illegible]terally; [illegible]rical [illegible]dity	T 99 F. P 54 BP 130/[illegible] WBC 8,[illegible]
38 J. P. 5/2/34	67 M W	Headache; drowsiness; mental confusion	0	5 mo.	0	+	0	+	0	0	0	0	+	0	0	Slight [illegible]p reflexes [illegible]ness of [illegible]eractive; left sid[illegible]teral	[illegible]binski [illegible]n	T 99 F. P 54 BP 130/[illegible] WBC 7,[illegible]
39 E. B. 5/12/34	53 F W	Headache	Struck head on bureau; 2 months	5 wk.	3 wk.	+	0	0	0	0	0	0	0	0	0	Genera[illegible] [illegible]p reflexes muscu[illegible]eractive weakne[illegible]terally; unable[illegible]teral Ba-stand	[illegible]ki sign	T 99 F. P 58 BP 130/[illegible] WBC 6,[illegible]
40 R. B. 6/23/34	62 M W	Headache; drowsiness; mental confusion	0	2 mo.	0	+	0	+	0	0	0	0	+	0	0	Genera[illegible] [illegible]p reflexes muscu[illegible]eractive weakne[illegible] unable[illegible] stand		T 98.6 F. P 56 BP 140/[illegible] WBC 6,[illegible]
41 E. A. 9/15/34	64 F W	Headache; drowsiness	Struck head on wall; 3 weeks	2 wk.	1 wk.	+	+	+	0	0	0	+ 24 hr.	0	0	0	0	[illegible]binski [illegible]n on [illegible]t	Not recorded
42 C. W. 10/31/34	47 M W	Headache; vomiting	In auto accident; unconscious; 3 months	5 mo.	0	+	+	+	+	0	0	0	0	0	Right vi[illegible] nerve palsy	Genera[illegible] [illegible]p reflexes weakne[illegible]e active unable[illegible]eft stand		T 99 F. P 66 BP 140/[illegible] WBC 10[illegible]
43 R. C. 11/20/34	8 M W	Headache; vomiting; photophobia	In auto accident; left eye discolored; 3 months	11 days	7 wk.	+	+	+	0	0	0	0	0	Bilateral [illegible]oss 1 D; hemorrhages	0	0	0	T 99 F. P 72 BP 90/60 WBC 8,[illegible]
44 A. H. 11/28/34	9 mo. M N	Drowsiness; convulsions	Fall from bed; 1 week	3 days	4 days	0	0	+	0	0	+	+ 24 hr.	0	Bilateral with hemorrhages	0	Right [illegible]eral weakn[illegible]binski (centr[illegible] type)		T 101 F. WBC 12,[illegible]
45 H. K. 2/9/36	17 M W	Headache; drowsiness	0	1 wk.	0	+	+	+	+	0	0	0	0	Bilateral 4 D with hemorrhages	0	Gener[illegible] [illegible] muscu[illegible] weakn[illegible] unabl[illegible] stand		T 100 F. P 48 BP 120/8[illegible] WBC 14,[illegible]
46 W. R. 3/3/36	55 M W	Headache; drowsiness	Fall on sidewalk; 6 weeks	6 wk.	2 days	+	+	+	+	0	0	0	+	0	Pupils sluggish	0	[illegible] reflexes [illegible]active [illegible]ht; [illegible]eral Ba-[illegible]ki sign	T 98.6 F. P 60 BP 170/1[illegible]
47 R. W. 9/5/36	38 M W	Headache, left and general; blurred vision; vertigo	Struck on head with brick; unconscious; 4 weeks	4 wk.	0	+	+	+	0	+	+	0	0	Bilateral 7-8 D	0	0	0	T 98.6 F. P 70-90 BP 120/8[illegible]
48 H. R. 7/9/37	59 M W	Headache; convulsion	Fall 8 weeks before admission; not unconscious	3½ wk.	2½ wk.	0	0	0	0	0	0	0	0	0	0	0	0	T 98.6 F. P 90 BP 150/1[illegible] WBC 8,0[illegible]

...ses of Subdural Hematoma—Continued

Reflex Changes	Temperature, Pulse, Blood Pressure, W.B.C.	Other Positive Findings	Roentgen Findings	Clinical Impression	Trephine Ventriculography	Side of Lesion Type of Operation and Date	Recurrence After Operation	Result	Comment
...binski ...n on ...ht	T 99.2 F. P 50 BP 90/50	Arteriosclerosis of peripheral and retinal vessels	Normal	Cerebral arteriosclerosis	+	Left craniotomy Aug. 2, 1932	0	Discharged well Aug. 14, 1932	Well in 1937
...binski ...n on right; ...le clonus ...right	T 100.6 F. P 80 BP 150/80	Arteriosclerosis of peripheral vessels	0	Subdural hematoma	Trephine disclosed hematoma	Left craniotomy Aug. 13, 1932 (membranes very thin)	0	Discharged well Aug. 23, 1932	Alcoholic; died in 1933 of stricture of esophagus
...p reflexes ...peractive ...erally; ...ical ...idity	T 99 F. P 54 BP 130/90 WBC 8,000	0	Normal	Subdural hematoma	Puncture	Left craniotomy; right subtemporal decompression; May 6, 1933	0	Discharged well May 23, 1933	Bilateral hematoma; well in 1937 save for slight degree of optic atrophy
...p reflexes ...peractive; ...teral ...binski ...n	T 99 F. P 54 BP 130/90 WBC 7,900	Arteriosclerosis of peripheral and retinal vessels	Normal	Tumor of the brain	Trephine disclosed hematoma, occipital	Left craniotomy May 3, 1934	Evacuation extra- and subdural hemorrhage; decompression May 4, 1934	Discharged well May 21, 1934	Well in 1937
...p reflexes ...peractive ...terally; ...teral Ba... sign	T 99 F. P 58 BP 130/80 WBC 6,600	0	Normal	Tumor of the brain	+	Left craniotomy May 15, 1934	Evacuation extra- and subdural hemorrhage; decompression May 16, 1934	Discharged well June 3, 1934	Well in 1937
...p reflexes ...peractive	T 98.6 F. P 56 BP 140/90 WBC 6,600	Arteriosclerosis of peripheral vessels	Normal	Tumor of the brain	+	Left craniotomy June 25, 1934	Evacuation extra- and subdural hemorrhage; decompression July 3, 1934	Discharged well July 9, 1934	Well in 1937
...binski ...n on ...t	Not recorded	Arteriosclerosis of peripheral vessels	0	Tumor of the brain	+	Left craniotomy Sept. 15, 1934	Evacuation extra- and subdural hemorrhage; decompression; Sept. 16, 1934	Discharged well Sept. 28, 1934	
...p reflexes ...e active ...left	T 99 F. P 66 BP 140/90 WBC 10,400	0	Normal	Tumor of the brain	+	Right craniotomy Nov. 2, 1934	0	Discharged well Nov. 12, 1934	History of some headache preceding auto accident by 2 months; well in 1937
	T290 F. P 72 BP 90/60 WBC 8,800	Tenderness to pressure left side of skull; cervical rigidity	0	Tumor of the brain	+	Left craniotomy Nov. 21, 1934	0	Discharged well Nov. 28, 1934	175 cc. fluid blood; few clots; hgb. 103%; RBC 4,100,000; WBC 6,100; NPN 28 mg.; NaCl 552 mg.; sugar 40 mg.; total protein 5.6; albumin-globulin ratio 65/35; well in 1937
...ral ...nski	T 101 F. WBC 12,000	0	0	Subdural hematoma	Puncture of subdural space	Left craniotomy; decompression; Nov. 30, 1934	0	Discharged well Jan. 3, 1935	Died in fire 2 months later
	T 100 F. P 48 BP 120/80 WBC 14,500	0	Normal	Tumor of the brain	+	Left craniotomy Feb. 11, 1935	0	Discharged well Feb. 20, 1935	Well in 1937
...reflexes ...active ...ht; ...ral Ba... sign	T 98.6 F. P 60 BP 170/100	Arteriosclerosis	Normal	Subdural hematoma	+	Left craniotomy Mar. 4, 1936; 12 hours later decompression	0	Discharged well Mar. 13, 1936	Small hematoma, 40 cc. blood laked; sugar 25 mg.; NPN 38 mg.
	T 98 6 F. P 70-90 BP 120/80	0	0	Subdural hematoma	+	Left craniotomy Sept. 8, 1936	0	Discharged well Sept. 16, 1936	Small hematoma, 40 cc. blood laked; NPN 28 mg. per 100 cc.
	T 98.6 F. P 90 BP 150/100 WBC 8,000	0	Normal	Subdural hematoma	+	Left craniotomy July 9, 1937	0	Discharged well July 21, 1937	Small hematoma, 40 cc. or less; no RBC in fluid

Sherwood's [18] in 1930, although in none of his cases was there a history of trauma. Peet and Kahn [19] in 1932 pointed out the importance of operative intervention in cases in which the patients are infants and children. Jelsma [20] in 1930 summarized the symptoms and clinical findings in 42 surgical cases previously reported in the literature and added 2 cases of his own. It is apparent that subdural hematoma is recognized more frequently than formerly, although the number of surgical cases reported is still rather small.

In the neurosurgical service of the Johns Hopkins Hospital between 1914 and 1935 there have been 48 cases of subdural hematoma in which the lesions at operation were found to have the characteristics of the traumatic hematomas described by others.[21] The first case was described by Heuer and Dandy [22] in 1916. That there may have been others in which the condition was unrecognized is likely only before the introduction of ventriculography by one of us (W. E. D.) in 1918. Prior to that time a right subtemporal decompression was frequently performed on patients suspected of having a tumor of the brain but not having localizing signs. The lesions in cases 2, 3 and 4 were apparently discovered during such an operation, and had the hematomas occurred on the left side it is readily seen that they would have escaped recognition. With the aid of ventriculography the diagnosis and localization of such a lesion has been greatly simplified.

Age.—Of the 48 patients 40 were adults, 6 were minors and 2 were infants each 9 months of age. The largest number of hematomas (11) occurred in the sixth decade of life, and the smallest number (3) occurred in the first decade. Five occurred in the second decade. That the lesion occurs occasionally in young persons has been recognized before. The average age for the entire group was 41.2 years. Jelsma in his analysis of 42 cases found an average age of 39.2 years and a fairly similar age distribution.

Sex.—There were 43 male and 5 female patients, a disproportion encountered in all other case reports and doubtless correctly attributed to the accepted cause, that is, trauma.

Color.—Forty-four patients were white, and 4 were Negroes.

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18. Sherwood, D.: Chronic Subdural Hematoma in Infants, Am. J. Dis. Child. **39**:980 (May) 1930.

19. Peet, M. M., and Kahn, E. A.: Subdural Hematoma in Infants, J. A. M. A. **98**:1851 (May 28) 1932.

20. Jelsma, F.: Chronic Subdural Hematoma: Summary and Analysis of Forty-Two Cases, Arch. Surg. **21**:128 (July) 1930.

21. Putnam, T. J., and Putnam, I. K.: The Experimental Study of Pachymeningitis Hemorrhagica, J. Nerv. & Ment. Dis. **65**:260, 1927.

22. Heuer, G., and Dandy, W. E.: A Report of Seventy Cases of Brain Tumor, Bull. Johns Hopkins Hosp. **27**:224, 1916.

Side of Occurrence of the Hematoma.—In 30 cases, or 61.7 per cent, the hematoma was on the left side, and in 15, or 32.1 per cent, it was on the right. In 2 cases, or 4.2 per cent, the lesion was bilateral. We can think of no reason for assuming that the much greater incidence of this lesion on the left side has any anatomic significance. In 1 case it lay about the sella turcica.

Cause.—That an injury to the head is generally regarded as the cause of this lesion has already been mentioned. Furthermore, the frequency with which subdural hemorrhages accompany severe injuries to the head has recently been emphasized by Leary [23] and Munro.[24] These authors and Coleman [16] included the "acute" lesions in their analysis of the subject. In this series, however, patients with fresh subdural clots, showing immediate symptoms of severe injury requiring prompt operative intervention, have been excluded because from a clinical standpoint they fall under the classification of patients suffering from the immediate effects of acute injury to the head.

TABLE 2.—*Age Incidence in Decades*

Age, Years	Number of Cases	Percentage
0-10	3	6.3
10-20	5	10.6
20-30	6	12.7
30-40	7	15
40-50	7	15
50-60	12	23.4
60-70	8	17
Average age, 41.2 years		

The incidence of trauma in this series was found to be lower than that recorded in most reports; a definite history of injury was obtained either before or after operation in 31 cases, or 65.9 per cent. In the other 17 cases, or 36.1 per cent, no history of even a trivial injury could be elicited despite our constant interest in this phase of the lesion. Furthermore, in the group of patients with a history of injury, the trauma was minor for exactly half of this number and might be considered major, in that consciousness was lost at the time, for the other half. Almost every type of accident has been described as giving rise to this lesion, particularly blows on the front and back of the head (Gardner [25]). It is of interest that 11 patients were injured in falls, 10 in automobile accidents and 4 in boxing; 3 accidentally bumped their heads on stationary objects, 1 was struck by a brick, 1 was kicked by a

23. Leary, T.: Subdural Hemorrhages, J. A. M. A. **103**:897 (Sept. 22) 1934.

24. Munro, D.: The Diagnosis and Treatment of Subdural Hematomata, New England J. Med. **210**:1145, 1934.

25. Gardner, W. J.: Traumatic Subdural Hematoma, Ohio State M. J. **31**:9, 1935.

horse and 1 was injured playing football. In only 2 instances was it doubtful that the trauma recorded could have been the cause of the hematoma. One patient (the patient in case 5) was injured three years before admission and at least one year before symptoms arose. In contrast, the patient in case 42 had a history of headaches and diplopia two months before he was rendered unconscious by an automobile accident. Among the 17 patients without a history of trauma, other possible predisposing factors, such as arteriosclerosis or alcoholism, were not of frequent occurrence. Only 2 patients had a history of alcoholism; both also had injuries. Of the 11 patients with clinical arteriosclerosis, 7 had injuries and 4 did not. It has been assumed by others that in such cases trauma has invariably occurred, although it may have been trivial and therefore forgotten by the patient. Whether or not this assumption is justified is open to question, but it would seem to be upheld by the fact that the clinical and operative findings in such cases are identical with those in cases in which there is a definite history of trauma.

Duration of Present Illness.—The present illness was of comparatively short duration in all but 2 cases. The patient in case 1 had been ill for fourteen months and was practically blind on admission. He also had been operated on elsewhere, a right subtemporal decompression having been done four months before. The patient in case 5 had a history of sick headaches for years, which were stated to have been worse for two years before admission; the time at which his other symptoms arose is not recorded. None of the other patients had symptoms of more than a year's duration. The shortest illness among the adults and minors was one week (case 36) and among the infants three days (case 44). The other infant, the child in case 9, was ill for five months. The average duration of the present illness for the entire group was thirteen weeks.

Latent Interval.—Of the 30 cases in which there was a history of trauma, a latent interval was present in only 14, or 43.3 per cent, the patients in the remaining 16 cases dating their symptoms from the time of the accident. In case 5 this period was a year (further evidence that the recorded injury was not the cause of the hematoma in this case), while in case 44 it was but four days. If these two extremes are excluded, the average length of this period was only three weeks.

Symptoms.—As noted by others, for the majority of patients with subdural hematomas the principal symptoms are those of intracranial pressure. Of the 46 adults and minors, 45, or 93.6 per cent, complained of headache, the patient in case 28 being the only exception. In but 5 cases was headache more pronounced on the side on which the hematoma occurred, while in 3 the opposite side was more affected. Headache, therefore, is of no value as a sign of localization. The next most

common complaint was drowsiness, occurring in 31 patients, or 66 per cent. Nearly the same number, 29, or 61.7 per cent, suffered from nausea or vomiting. Vertigo, apparently arising with changes in position, was recorded for 16, or 34 per cent. Only 13 patients, or 27.6 per cent, had diplopia, and 10, or 21.2 per cent, had periods of mental confusion. Weakness of one side of the body was a principal symptom for only 3 patients, or 6.3 per cent, and the same number complained of tinnitus. Convulsions occurred in 7, or 12.7 per cent. Both infants, the patients in cases 9 and 44, had generalized convulsions. Of the 5 adults, the patients in cases 29 and 34 had focal seizures and those in cases 35 and 47 and 48 had generalized convulsions. The patient in case 15 was epileptic but had no attacks during the present illness. Visual failure was complained of in 2 instances. The patient in case 1 was nearly blind with a high grade of papilledema. This was the only patient with a history of progressve deafness. The patient in case 24 was totally blind. The case of this patient was the most unusual in the series and has previously been reported by one of us (W. E. D.[26]). The visual failure and associated atrophy of the optic nerve were due to direct pressure on the optic chiasm by a hematoma surrounding the sella turcica (fig. 1). In summary, a history of symptoms possessing localizing value was obtained in but 5 cases, or 10.6 per cent (cases 8, 14, 28, 29 and 34).

Objective Findings.—For most of the patients the clinical findings were indicative of intracranial pressure only. Papilledema was present in 25, or 53.2 per cent, and absent in 21, or 44.7 per cent. Associated retinal hemorrhages occurred in 7, or 14.8 per cent. The degree of papilledema varied from less than 1 diopter to 6 diopters, with little difference on the two sides. No significant abnormalities of the visual fields were recorded. In no instance was there hemianopia. The patient in case 24, who has been mentioned, was the only patient with atrophy of the optic nerve. Central facial weakness was present in 8 cases (17 per cent), being an isolated finding in 4. Three patients (6.3 per cent) had nystagmus, and 2 (4.4 per cent) had ptosis. The patient in case 30 had bilateral ptosis, sluggish pupils and inability to look upward, while the patient in case 21 had unilateral ptosis corresponding to the side on which the hematoma was present. Anisocoria was noted in a single case (33), the larger pupil being on the same side as the hematoma. The corneal reflex was absent in 2 cases (4.4 per cent). In case 25 it corresponded to the side on which the hematoma occurred, whereas in case 37 it was also unilateral although the hematoma was bilateral. Cases 1 and 24 were the only instances of marked reduction in vision, the

26. Dandy, W. E.: The Brain: Subdural Hematoma, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12, chap. 1, p. 299.

patient in case 24 being blind. Of the remaining cranial nerves, none except the sixth was recorded as abnormal.

General muscular weakness was a rather frequent observation, 8 patients, or 17 per cent, being unable to stand unassisted. Weakness of the extremities on one side also occurred in 8 cases, being marked in only 2, cases 8 and 14. Interestingly, this hemiparesis occurred on the same side as the hematoma in 2 cases (cases 6 and 38). Case 31 was the only instance of hemihypesthesia. Astereognosis was not noted in a single case.

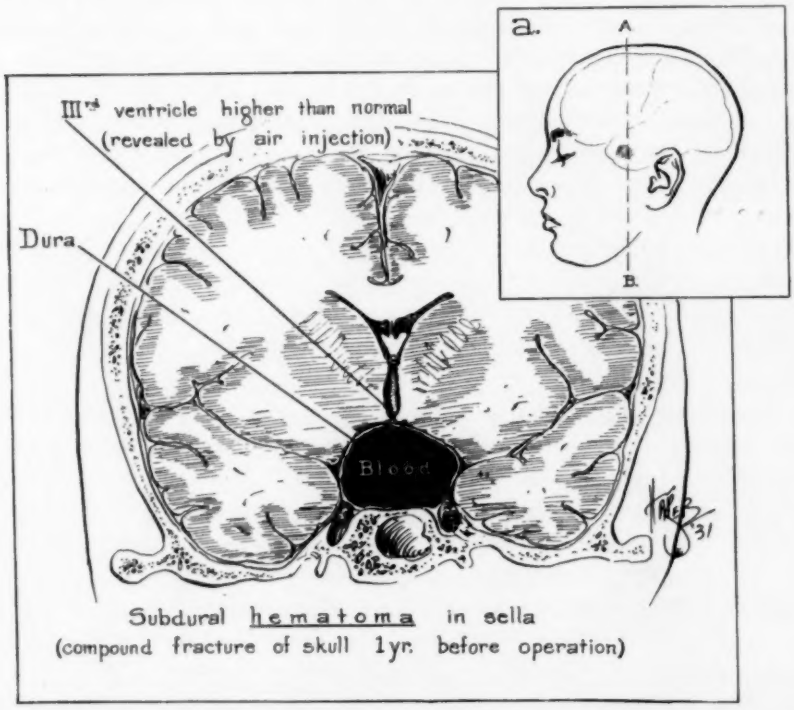

Fig. 1.—Post-traumatic subdural hematoma about the pituitary body in case 29. This patient had signs of a hypophysial tumor, including destruction of the sella turcica.

The reflexes were more frequently disturbed. The deep reflexes were bilaterally hyperactive in 9 cases, or 19.2 per cent, and unilaterally more active in 14 cases, or 30 per cent. In case 21 this hyperactivity occurred on the same side as the hematoma, while in case 17, with unilateral activity, there were bilateral hematomas. The Babinski sign was recorded in 20 cases, 44.6 per cent; it was bilaterally present in 12 cases, or 27.6 per cent, and unilaterally present in 8 cases, or 17 per cent. In cases 6 and 7 the Babinski sign occurred only on the side on

which the hematoma was present. It is significant that Fleming and Jones,[10] Frazier [15] and Kaplan [9] have noted the presence of homolateral neurologic findings, the last-named author having observed them in 5 of 8 cases. Another reflex which occurs occasionally in the presence of a tumor of the brain, namely, cervical rigidity, was observed in 3 cases (6.4 per cent).

The frequency with which a history of drowsiness was obtained has already been recorded, but it is worthy of note that 8 patients, or 17 per cent, were in coma at the time of admission and required immediate operation. Although mental confusion was recorded for 10 patients, and although a majority of the hematomas were on the left side, the patient in case 14 was the only one showing motor aphasia.

In summary, then, if one considers the reflex changes having value in the localization of the cerebral lesion and the presence of motor weakness, sensory loss and aphasia, one finds that 25 patients, or 53.2

TABLE 3.—*Symptoms in Order of Occurrence*

Symptom	Number of Cases	Percentage
Headache	44	93.6
Drowsiness	31	66
Nausea and vomiting	29	61.7
Vertigo	16	34
Diplopia	13	27.6
Mental confusion	10	21.2
Convulsions	7	12.7
Weakness on 1 side of body	3	6.3
Tinnitus	3	6.3
Failing vision	2	4.2
Failing hearing	1	2.1
Numbness of 1 side of body	1	2.1

per cent, were without positive findings, 19 patients, or 40.3 per cent, possessed them in part, and 3 patients, or 6.7 per cent, showed neurologic findings referable to the uninvolved hemisphere.

Elevation of temperature above 101 F. occurred in but 2 instances (cases 3 and 8). On the other hand, in 7 cases, or 15.5 per cent, there were leukocyte counts of more than 12,000; in cases 3, 9, 15 and 20 there was leukocytosis, the leukocyte count ranging between 15,000 and 20,000. Such a high leukocyte count is fairly common in association with subdural hydroma. Of greater significance was the pulse rate before operation. Twenty-six patients, or 55.3 per cent, had bradycardia, the pulse rate being 60 or below; 9, or 19.1 per cent, had a pulse rate between 60 and 70, and only 8, or 17 per cent, had a pulse rate above 70. In 4 cases, or 8.8 per cent, the rate was not recorded prior to operation. The only other positive physical findings of note were also in the cardiovascular system. Arteriosclerosis of the peripheral or retinal vessels was noted in 10 cases (21.2 per cent), and 10 patients had a blood pressure of 140 systolic and 90 diastolic (or higher). It is interesting that the patient in case 9, an infant, had an enlarged head

and separation of the sutures suggesting hydrocephalus. The other infant (case 43) had a head of normal size with bulging fontanels and was in coma. Both had generalized convulsions.

Most of the laboratory studies gave negative results. The Wassermann reaction of the blood was negative in every case. Lumbar punctures were done on the 2 infants, 1 of whom (case 9) had normal fluid and the other (case 43) xanthochromic fluid, apparently the most common abnormality occurring in association with this lesion. Only in case 4 did the roentgenograms show a fracture of the skull.

Clinical Diagnosis.—From what has been recorded concerning the histories of this group of patients it is not surprising that a presumptive diagnosis of subdural hematoma was made in only 12 cases, or 23.3 per cent. Twenty-nine patients, or 61.7 per cent, were thought to have a

TABLE 4.—*Neurologic Findings*

	Number of Cases	Percentage
Papilledema	25	53.2
Retinal hemorrhages	7	14.8
Atrophy of the optic nerve	1	2.2
Facial weakness (central)	8	17.0
Nystagmus	3	6.6
Ptosis	2	4.4
Anisocoria	1	2.2
Absence of corneal reflex	2	4.4
General weakness	8	17.0
Hemiparesis	8	17.0
Hemihypesthesia	1	2.2
Hyperactive deep reflexes (bilateral)	9	19.2
Unilaterally hyperactive deep reflexes	14	30.0
Bilateral Babinski sign	12	27.6
Unilateral Babinski sign	8	17.0
Cervical rigidity	3	6.4
Coma	8	17.0
Aphasia	1	2.2

tumor of the brain; 2 patients, or 4.2 per cent, were thought to have abscesses of the brain, and for a similar number the condition was diagnosed as cerebral hemorrhage. The condition of 1 patient (2.1 per cent) was diagnosed as hydrocephalus and that of 1 as arteriosclerosis of the brain. Because of the presence of blindness and atrophy of the optic nerve the patient in case 24 was believed before operation to have a tumor of the pituitary gland. Clinical differentiation between the manifestations of subdural hematoma and those of tumor of the brain is especially difficult because of the common tendency of patients to attribute their symptoms to injuries.

VENTRICULOGRAPHY

Since an unlocalized tumor of the brain is suspected in a high percentage of cases of subdural hematoma, the localization of the lesion is ultimately dependent on ventriculographic examination or its equivalent, direct puncture of the hematoma. A subdural hematoma cannot escape

detection by ventriculographic study and not infrequently the exact character of the lesion can be determined from the ventriculograms alone.

In our series of cases only the ventricular injection of air has been used. This is certain and safe, and the results are absolute. Unless there are undoubted signs of localization (and in few of these cases was this true) a surgeon will no longer take chances on finding the lesion through an operative exposure of the brain. Subdural hematomas are therefore (with only rare exceptions) localized by ventriculographic study. The spinal route for injection of air has not been used because it entails unnecessary danger and the results are capricious. In approximately one third of all spinal injections the air injected into the spinal canal will not reach the ventricular system, because the foramen of Magendie is not patent and air cannot pass through the foramens of Luschka. It is interesting in this connection that Van Dyke [27] has localized a hematoma by the subarachnoid picture of the air and regards the findings as pathognomonic.

When there is a history of recent trauma and the diagnosis of subdural hematoma is a probability or even a possibility, the openings for the ventricular puncture are regularly made anteriorly, i. e., over the anterior horns of the lateral ventricle instead of at the usual posterior site. In addition, the bony opening, instead of being made solely by a perforator, is enlarged by a burr in order that the color of the dura may be better seen and the dura may be carefully inspected as it is opened in search of a hematoma. If the dura is punctured blindly through a conical perforator opening in the bone, one may easily mistake the blood of a punctured superficial cerebral vein for that of a subdural hematoma; with a perforator opening enlarged by means of a burr, this mistake is not possible, for with such an opening one can actually see the outer membrane lining the inner surface of the dura, and if a hematoma does not exist the cortex will present. The reason for making the bony openings anteriorly is that the hematoma will usually be encountered at that point, for with occasional exceptions it extends to the midline. Frequently the hematoma ends slightly anterior to the usual site of the posterior openings, and it would be missed if the puncture were made in the occiput. There are cases in which the anterior opening also just misses a subdural hematoma. The mesial border of this lesion may be irregular, reaching the falx only in part of its course, and in one of its outward bends the dural puncture may just miss the hematoma. The only advantage in reaching a hematoma directly is the avoidance of an injection of air. If a hematoma is not

27. Van Dyke, C. H.: A Pathognomonic Encephalographic Sign of Subdural Hematoma, Bull. Neurol. Inst. New York **5**:135, 1936.

encountered the wounds are closed, and ventriculographic examination is completed in the usual fashion.

Another advantage of the anterior openings is that the occasional bilateral hematoma may be disclosed without the necessity of ventriculographic study. Moreover, in such cases it is highly probable that both lateral ventricles will be nearly or entirely obliterated by the space-occupying lesions, so that ventricular puncture is difficult or even impossible. In both of our cases in which the condition was bilateral the double lesions were disclosed solely by anterior puncture.

In 27 cases, or 57.7 per cent of the series, ventriculographic studies were made prior to operation. In 7 others, or 15.5 per cent, prepara-

TABLE 5.—*Summary of Findings in Ventriculograms from Cases of Subdural Hematoma*

Do Both Ventricles Contain Air?	Is There Contralateral Hydrocephalus	Anteroposterior View		Contralateral Ventricle Compressed	Lateral View	
		Sharp Upper Cut in Ventricle	Concavity of Outer Border		Homolateral Ventricle Reduced in Size	Filling Noted in Contralateral Ventricle
+	+ Small rounded	+	+	Slight	Entire ventricle but more in anterior horn and body	None
+	+ Slight	+ Slight	+ Slight	No	Anterior half reduced; posterior absent	+
Only contralateral	+ Slight	Not filled	Not filled	+	Ventricle obliterated	None
Only contralateral	+ Big	Not filled	Not filled	..	Ventricle obliterated	+
+	No	+	+	No	Only shred of posterior half; anterior reduced	None
+	No	+	+	No	Only slight remains	+
Only contralateral	+ Posteriorly; small anteriorly from compression	Not filled	Not filled	+	Ventricle obliterated	None

tions were made for ventriculographic examination but the hematoma was encountered when the dura was punctured en route to the ventricle. Of the total number of cases, therefore, ventriculographic examination or its equivalent was required in 75 per cent. These figures, however, do not portray the actual facts in this regard, for 5 of the cases were observed before the introduction of ventriculography in 1918. Since this time the occasion is rare indeed when ventriculographic study or its equivalent is not deemed necessary. Since 1918 these tests have been used in 64.3 per cent of cases. In 18 air was present in the third ventricle and in both lateral ventricles. In 9 cases the lateral ventricle on the side on which the hematoma was present did not contain air. In every case air reached the third ventricle, which was markedly oblique.

VENTRICULOGRAPHIC FINDINGS

For several years it has been evident that the ventriculographic plates will frequently disclose a change in the ventricular system that is pathognomonic. From the ventriculograms alone, therefore, one can frequently make the diagnosis of subdural hematoma even though the history may have offered no suggestion of this lesion. To know that the intracranial lesion is a subdural hematoma and not a tumor is of the greatest importance to the operator and the patient, for the extent of the cranioplastic procedure is reduced by half and the position of the bone flap is changed.

In general it may be said that the changes demonstrable by ventriculography in cases of subdural hematoma closely resemble those in cases of dural endothelioma, which are almost but not quite pathognomonic. A dural tumor is recognized by the sharp, straight line that represents the border of the growth in the deformed ventricle. This is particularly evident in the anteroposterior view, which shows the lateral ventricle in cross section. A subdural hematoma produces a precisely similar ventricular change, i. e., a sharp, straight ventricular defect which is always on the superior surface of the affected ventricle (in cross section); and, in addition, it usually but not invariably induces a concave indentation on the outer surface of the lateral ventricle (in cross section). That both the superior and the outer surface of the ventricle are affected is due to the extensive distribution of the hematoma; i. e., it is both superior and lateral to the ventricle. Such a bilateral effect on the ventricle is occasionally seen with a large dural tumor, but this is infrequent. The third important ventriculographic change is seen in the lateral view. Since the hematoma usually extends from the frontal to the occipital pole, the lateral ventricle is correspondingly compressed so that the resultant ventriculographic picture shows a lateral ventricle greatly reduced in size throughout most of its horizontal extent, i. e., from the anterior horn through the body to and not infrequently including the posterior and descending horns. This again is a picture that is occasionally but uncommonly reproduced by a cerebral tumor. We have occasionally seen the aforementioned ventriculographic deformations caused by cerebral tumors surrounded by extensive cerebral edema; the findings are therefore not absolute.

The ventriculographic changes in both lateral and anteroposterior views taken in our last 9 cases are shown in the accompanying sketch (fig. 2). The pneumographic shadows have been traced from the roentgen plates. All of our earlier ventriculograms were destroyed when the inflammable roentgen plates were superseded by the modern ones that do not burn.

Ventricular changes on the side on which the lesion was present were as follows:

1. Anteroposterior view.

(*a*) In all instances there was dislocation of the ventricular system to the contralateral side.

(*b*) With one exception (*G*) the anterior horn in cross section was smaller on the side on which the lesion is present. In this instance it was about twice as large on the affected side. Why this exception

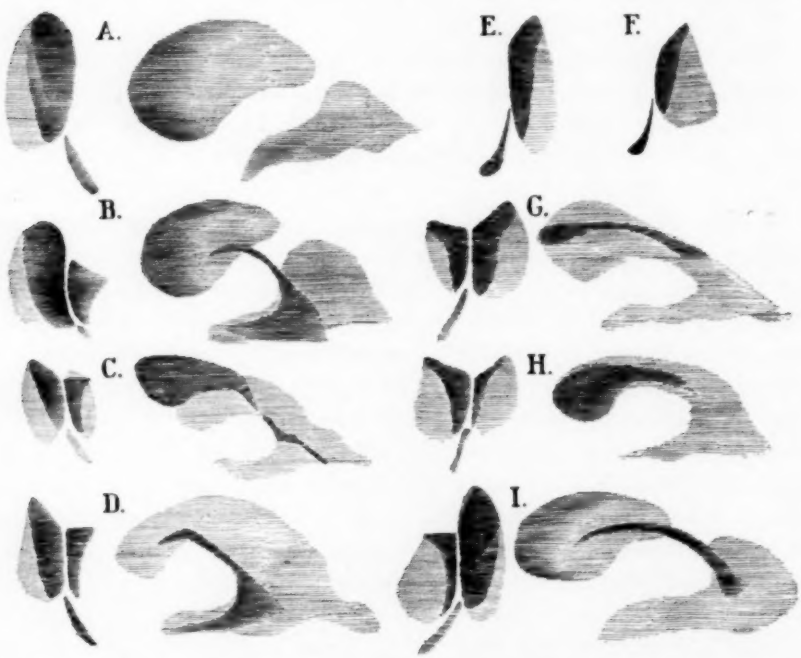

Fig. 2.—Shadows traced from ventriculograms taken in 9 cases of subdural hematoma. See text for explanation.

occurred we do not know. In the remaining cases the ventricle on the side on which the lesion was present varied in size from slightly smaller than the other to complete absence in 3 cases (*C*, *F*, and *I*).

(*c*) The telltale sharp upper border was present in 4 and absent in 2 of the affected ventricles that filled.

(*d*) The equally telltale concave lateral border was also present in 4 and absent in 2 of the affected ventricles that filled. The absence of these nearly pathognomonic changes in the ventricles is doubtless due to the lesser volume of the hematoma over the frontal region in these cases.

(*e*) The all-important obliquity of the third ventricle was well defined in every instance.

(*f*) In two plates the shadow of the third ventricle was strikingly club shaped (and in two others the change was present but less pronounced), rounded inferiorly and gradually flattening to an acute angle superiorly. This effect was due to the varying degree of pressure from the hematoma in the upper (greater) and the lower (lesser) end of the ventricle. It is hardly probable that this deformation has any relation to subdural hematoma.

2. Lateral view.

(*a*) Without exception the lateral ventricle in all cases was tremendously reduced in size throughout its longitudinal extent. The reduction in the ventricular volume may be greater in front, greater behind or essentially equal throughout. The character and extent of the reduction may be seen in fig. 2. In 3 cases (33.3 per cent) the ventricle was entirely collapsed on the affected side.

Ventricular changes on the contralateral side were as follows:

1. Hydrocephalus of varying degree was present in 6 of the 9 cases. It was advanced in 3 cases, slight in 3 and absent in 3. The cause of hydrocephalus was compression of the aqueduct of Sylvius. The lesser degree of hydrocephalus was diagnosed from the anteroposterior view when the corners of the ventricle were rounded; this is always the earliest objective evidence of ventricular dilatation. The moderate degree of hydrocephalus leads us to believe that in these cases occlusion of the aqueduct was partial and was of the ball valve type.

2. A partial filling defect about the middle of the contralateral ventricle was present in 2 cases (lateral view). This was due to the fact that the maximum volume of the hematoma compressed the opposite ventricle in this region. The greater obliquity of the third ventricle is also evidence of the great compression effect in this transverse plane.

3. Flattening of the anterior horn was definite in 2 cases (figs. 2 *C* and 2 *I*) and probably present in slight degree in a third (fig. 2 *A*, anteroposterior view).

PATHOLOGIC PICTURE

The striking pathologic findings in cases of subdural hematoma are:

1. A large collection of dark fluid blood is present, with a few soft brownish yellow clots dangling from the outer membrane but sometimes extending across and attached to both membranes.

2. The fluid blood when left standing in a test tube will never clot, even when normal blood is added to it; i. e., the clotting element has been completely eliminated.

3. The blood is hermetically sealed in membranes that cannot extend; the hematoma is therefore not progressive.

4. The outer membrane is always thick (1 to 4 mm.); it is snugly attached to the dura but can be stripped from it; it is opaque and fairly vascular. Its vascularity is derived from the dura, from which new vascular channels connect with newly formed blood spaces in the membrane.

5. The inner membrane is thin, transparent and avascular. It lies loosely on the pia-arachnoid, but there is no attachment except at the margins of the hematoma, where the inner and the outer membrane are confluent; in this region there may be a firm line of attachment to the brain.

In this series the volume of the hematoma was estimated to have varied from 1.3 ounces (40 cc.) to 8 ounces (240 cc.). In case 9, 80 cc. of old blood was aspirated; in case 43, 175 cc. of fluid blood was removed from the sac, and in addition there were several fair-sized clots; in cases 46 and 47 the contents of the sac were entirely fluid and measured but 40 cc. Except for the lesions in cases 16 and 24, the hematomas were described as lying on the frontal and parietal lobes and frequently on the occipital lobe; they extended from the longitudinal sinus to the region of the sylvian vein. In 1 instance the hematoma was exclusively in the temporal region; it was directly over the site of a blow, and beneath it the brain was excavated from absorption of the contused area. In another case the hematoma was in the sella turcica, causing the sellar contents to bulge and act like a tumor. In 1 case (case 26), associated with the hematoma but separate from it was a subdural hydroma (fig. 3). In no instance have we been able to determine the source of the blood. In case 16 it seemed probable that a large thrombosed vein crossing from the atrophic defect in the temporal lobe to the dura may have been the source of the original bleeding, but there is, of course, no proof.

The condition of the blood within the membranes is of interest. That such blood no longer has power to clot is doubtless due to the extraction of the clotting substance in the formation of the outer membrane. That there remain a few small and seemingly degenerative clots within the hematoma indicates that there has originally been clot formation; it would be difficult to believe that the blood had not quickly clotted in the beginning. But why should the new tissue representing the outer membrane develop exclusively along the dura and not form throughout the volume of blood, as in Virchow's pachymeningitis interna? And why, too, should it never form on the arachnoid membrane? The fact that the dura is vascular unquestionably accounts for

the growth of vascular channels within the outer membrane, but hardly for its thickness, which is fairly uniform, or for its intrinsic character. That the inner membrane is not caused by any derivative of the blood is shown by the fact that precisely the same membrane forms in cases of subdural hydroma, in which, of course, no blood is present. One can therefore only conclude that the membrane is a product of reaction of the pia-arachnoid. It is also worthy of interest that exactly the same thin, transparent membrane is present on the dural side of a subdural hydroma, although as time advances it becomes somewhat thicker and more opaque than the inner membrane, and it too adheres tightly to the dura.

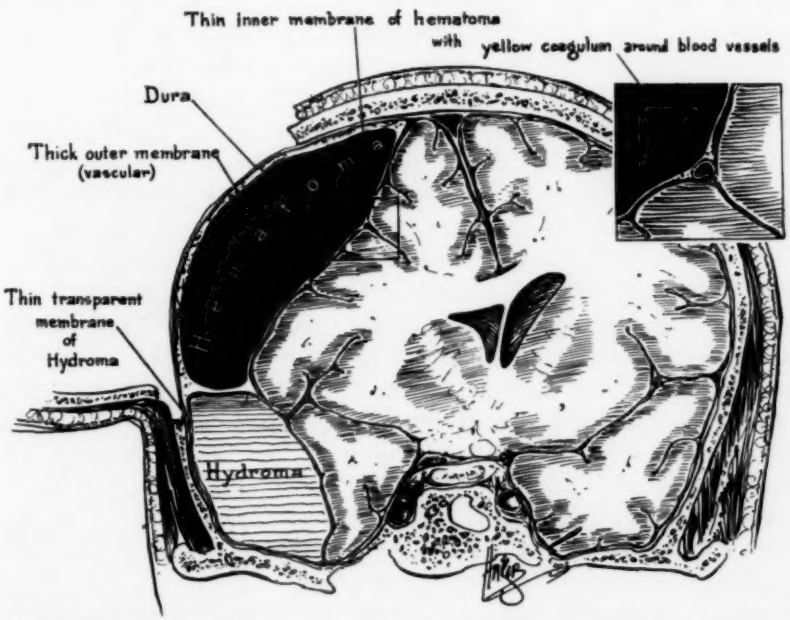

Fig. 3.—Subdural hydroma coexisting with a subdural hematoma in case 26. Both resulted from the same injury.

Can a subdural hematoma disappear spontaneously? This hardly seems possible, because the limiting membranes can scarcely absorb blood. Although vascularized, the inner surface of the outer membrane is smooth and glistening from pressure alone. We have never seen, either at operation or at necropsy, a hematoma as late as a year after its origin (except one solid clot, in case 18). This fact, together with our clinical experience, leads us to doubt that survival is possible after this time. Most of the patients that come for operation appear at a time when on account of advanced intracranial pressure the tenure of life is unquestionably short. These statements naturally lead us to doubt,

and even to deny, that Virchow's pachymeningitis is the same lesion as the subdural hematoma, even though the end result of Virchow's lesion as seen at necropsy might well lead one to assume that a large hematoma has become absorbed and replaced by fibrous tissue.

One of the most surprising findings in cases of subdural hematoma is the gross and microscopic appearance of the blood. The blood when viewed in bulk is black, but venous blood is also dark, and when the specimen is small and unless specimens of the blood from the different sources are side by side it may be difficult to tell from inspection alone that the blood is unquestionably that of a hematoma. Even when a small amount of blood from a subdural hematoma is placed on a white towel at operation and its color compared with the color of venous and arterial blood from the scalp and the dura it may be difficult to be certain that the blood from the hematoma is actually different. Usually, however, the hematomatous blood when spread on a white background is rusty brown, in contrast to the red of fresh blood. The difficulty in being absolutely certain led us to inspect the dura and the outer membranes directly through a burr opening rather than through the smaller perforator opening used for a ventricular or cerebral puncture. On one occasion a specimen of blood had been obtained through a smaller bony opening through which the dura could not be inspected. The appearance of the specimen and its color on the towel were such that a competent physician insisted that the blood was from a punctured vein; and even when the specimen was examined under a microscope most of the corpuscles were found to be well rounded or only slightly crenated—and this after being free for a period of several weeks in the cranial chamber!

Other amazing features of subdural hematoma are that it is nearly always located in the same region and that the brain almost never shows any signs of injury. Only in case 16 was the brain injured; this case presented also one of the two exceptions to the usual location, the lesion being in the temporal region. In this instance the brain was lacerated and excavated, and bridging vascular trunks crossed the defect. Except for these features the resultant hematoma was precisely similar to the remaining ones in the series. Since the hematoma almost invariably begins at the midline of the cranial chamber and spreads outward, since the outer membrane is thickest along the midline, since there are no torn veins over the surface of the brain and since the large cerebral veins are most exposed where they "jump" across from the cerebral hemisphere to the longitudinal sinus, the only conceivable explanation for a hematoma is rupture of one of these crossing veins. The bleeding would almost necessarily be into a potential cavity, and this does exist along the falx. Venous bleeding elsewhere would, with rare exceptions, be quickly stopped spontaneously by the apposi-

tion of tissues. Moreover, arterial bleeding could scarcely be responsible, for the only arteries in this region are in the substance of the brain, and the brain is practically always uninjured. Then, too, spontaneous cessation of arterial bleeding just short of severe intracranial pressure at the time would be far less probable as a consistent outcome. It might happen occasionally, but not repeatedly. One other exception to the almost uniform picture of this lesion should be noted. In 1 case (case 18) the hematoma was entirely solid and could be shelled out like a tumor and there were no membranes. In case 43 the hematoma was in large part solid.

Why this difference exists we do not know. Whether subdural hematoma uncomplicated by other factors ever causes death at once is not certain. Certainly in a high percentage of cases the danger has been little at the time and symptoms have developed a few weeks or months later. It is the progressive nature of the symptoms that has led to the widespread belief that the hematoma itself is progressive. This is, of course, precluded by the rigid and unchanging walls of the hematoma. What, then, causes the progressive symptoms and eventually death? That intracranial pressure is the cause cannot be questioned, because its relief brings immediate preservation of life. It is hardly believable that the volume of fluid blood in the hermetically sealed capsule which precludes absorption can become greater. Nor is it conceivable that new hemorrhages can occur within the rigid walls, because there are no exposed vessels that can bleed. The answer we believe to be in the reaction of the brain to the hematoma as a foreign body. We know that tremendous areas of cerebral edema surround tumors of the brain and that this occurs in variable degrees with different tumors. We also know that patients with tumors of the brain and other lesions causing intracranial pressure may be physically entirely well one minute and unconscious or dead the next from sudden strain or from a cough or even with no recognizable predisposing cause. The sudden change is due to increased cerebral edema and not to hemorrhage into the tumor. Precisely the same factors, we believe, are responsible for the gradual progression of subdural hematoma and the eventual death of the patient, i. e., the reaction in the brain from a lesion that already occupies a volume so great that the margin of security at any time is slight.

In only 3 cases was any study made of the cellular and chemical constituents of the blood. In case 26 a red blood cell count showed 5,000,000 cells per cubic centimeter. In case 43 the hemoglobin percentage (Sahli) was 103, the red blood cell count 4,100,000 per cubic centimeter and the white blood cell count 6,100 per cubic centimeter. A smear stained by the method of Wright showed the cells to be

normal in appearance but with an apparent absence of platelets. Chemical analysis showed a nonprotein nitrogen content of 28 mg. per hundred cubic centimeters, a sodium chloride content of 552 mg. and a sugar content of 40 mg. The total protein content was 5.6 mg. per hundred cubic centimeters, and the albumin-globulin ratio, 65:35. The hematomas that occurred in cases 46, 47 and 48, which were relatively small, measuring approximately 40 cc. each in contrast to the hematoma in case 42 measuring 175 cc., contained blood which was entirely

Fig. 4.—Photomicrograph of the outer membrane from the subdural hematoma in case 43. Note the relatively large number of newly developed blood vessels among the new connective tissue cells.

laked, as no red blood cells could be demonstrated in preparations. The nonprotein nitrogen content was 38 mg., and the sugar content, 25 mg., per hundred cubic centimeters. From this evidence alone the theory of gradual enlargement of the hematoma from repeated hemorrhages from the membranes, first proposed by Virchow,[2] and the more recent theory of Gardner,[12] McKenzie [11] and Zollinger,[28] that the hema-

28. Zollinger, R., and Gross, R.: Traumatic Subdural Hematoma, J. A. M. A. **103**:245 (July 28) 1934.

toma enlarges by the acquisition of fluid from the subarachnoid spaces by osmosis, are both seen to be impossible. What is more probable is that, whereas the patient's symptoms are progressive, the hematoma is actually regressive after the initial period of hemorrhage. The absence of severe symptoms accompanying the original hemorrhage is probably due to the fact that it is venous and not arterial in origin. Furthermore, microscopic sections from the inner and outer membranes of the sac in all the cases in which operation was done [6] showed them to be composed of granulation tissue containing numerous capillaries, especially in the

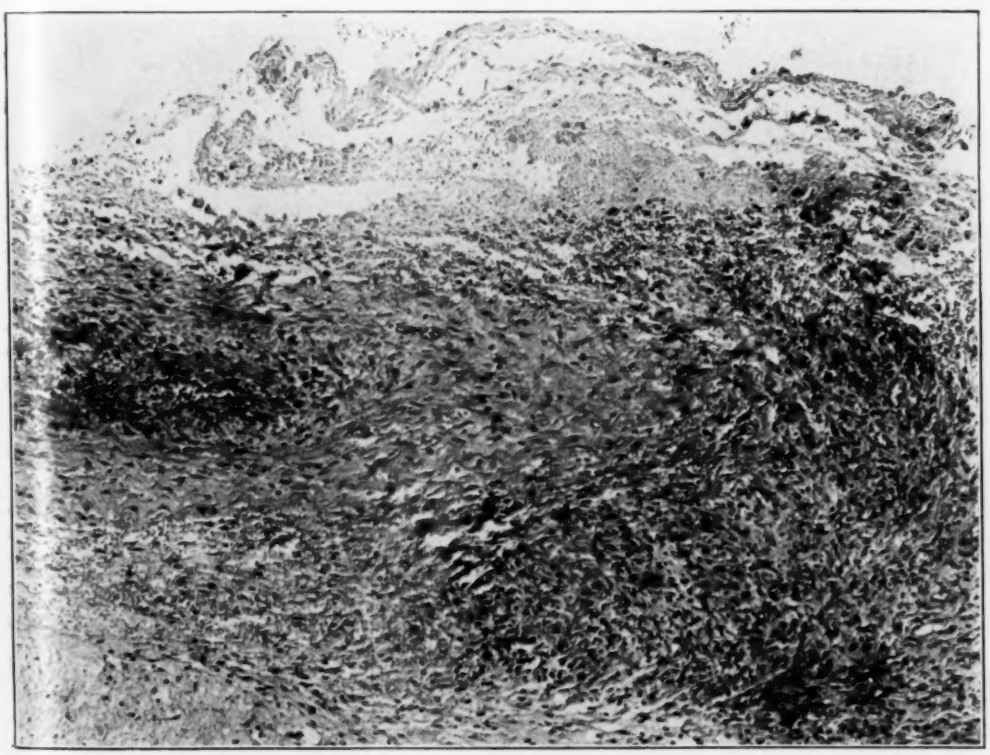

Fig. 5.—Photomicrograph of the inner membrane in case 15. The membrane shows principally a large layer of unorganized fibrin, with relatively few connective tissue cells and blood vessels.

outer membrane. Both membranes were infiltrated with leukocytes, particularly the outer membrane. There were also occasional interstitial hemorrhages (figs. 4 and 5). In no case was there evidence of any mesothelial-lined spaces as described by Cushing and Putnam.[1]

TREATMENT

Obviously the only treatment is surgical. Although repeated aspirations of a subdural hematoma have been advocated, our experience

with 1 hematoma so treated was the least satisfactory of the series; the patient recovered completely but required repeated tappings for three months. A decompression had been made, and its fulness indicated the need for the repeated relief of pressure. Our plan of attack in recent years has consistently been to turn down a very small bone flap (fig. 6), excise with the electrocautery the outer membrane flush with the dural incision and strip the thin, avascular and unattached inner membrane as far as possible from the surface of the brain. We irrigate the hematoma from the cranial chamber by flushing with Ringer's solution. Not infrequently one or more isolated pockets of blood exist

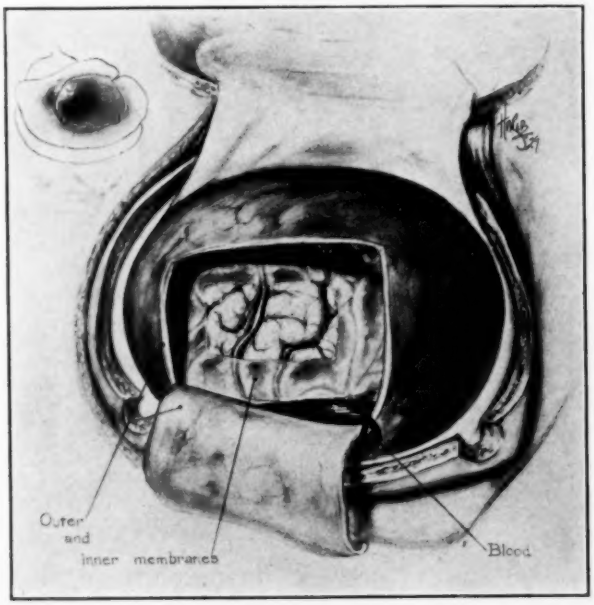

Fig. 6.—Operative view of a subdural hematoma, with windows in thicker outer membrane and thinner inner membrane. The intact brain lies beneath. Blood fills the space between the membranes. The hematoma usually covers most of the outer surface of the cerebral hemisphere.

in the subdural space. Careful inspection of this space will disclose them bulging into the large primary cavity. They are punctured, evacuated and irrigated; it has not been necessary to remove any of their covering membranes.

Whether or not removal of the inner and outer membranes is necessary cannot be stated. Since only a fraction of the entire surface area is removed and cures are unequivocal and prompt, we have gradually lessened the size of the cranial exposure and have seen no difference in the immediate or ultimate results. It is largely for this reason that the preoperative differential diagnosis of a subdural hematoma is impor-

tant. If a hematoma is still questioned after ventriculographic studies have been made, a burr opening in the line of the proposed cranial approach is inspected before the incision is made. If a hematoma is discovered in incising the dura an osteoplastic flap of approximately half the size of that necessary for a tumor will answer every purpose and correspondingly reduce the severity of the operation.

In this series the chief postoperative complication was hemorrhage, subdural or extradural or both; this occurred in 16 cases, or 34.2 per cent. In 15 of these an osteoplastic flap had been employed, and it was necessary in 2 instances to evacuate the hematoma a second time. It is interesting that on this second exposure the blood was always clotted. In case 10, in which operation was done by the subtemporal route, evacuation of the hematoma through a superimposed craniotomy opening was required. Also, the patient in case 46, with a very small hematoma, showed signs of intracranial pressure in twelve hours, owing to cerebral edema alone; he was rescued by a decompression.

The principal source of subdural postoperative bleeding is the raw edge of the outer membrane of the sac, which is fairly vascular. Bleeding from this source can now be prevented by incising the membrane by the cutting current of the electrocautery. Because of the great vascularity of the outer membrane it is important that it be not stripped from the dura beyond the dural defect, where oozing would be out of reach. Extradural bleeding is the source of greater concern than is bleeding beneath the dura. With meticulous care this can now be avoided; at least the incidence will be very low if the dura is completely incised parallel to and near the bony margins, the dura drawn tightly to the skull by several sutures and the bone largely stripped of its blood supply. Failure of the affected hemisphere to expand after operation in the absence of hemorrhage occurred in 1 case; it was overcome by placing the patient in the head-down position for twenty-four hours and by adding fluids to the circulation. Important in the postoperative care was the release of fluid and air from the subdural space by occasional tapping with a ventricular needle during the first forty-eight hours.

The danger of postoperative bleeding is scarcely less and may be even greater than that of the original hematoma; it would usually quickly end in death if not immediately recognized and promptly treated by reopening of the wound and evacuation of the clot. The detection of a postoperative hematoma requires constant and careful observation of the patient, the state of consciousness being by far the most important item. If the lesion is detected early the reopening of the wound entails no risk; if the discovery is delayed the risk increases rapidly. As most patients are very drowsy and even comatose at the time of operation, a few hours' delay in recognizing a postoperative hematoma may well cause the death of the patient. The low mortality rate in the series is

evidence of the careful study of patients by the resident surgeons. Failure to discover a postoperative hematoma is a fault scarcely to be forgiven.

The unusually high incidence of postoperative bleeding with this lesion has often led us to wonder if there may be some predisposing tendency to bleed. This probably is not so. With anesthesia induced by means of avertin with amylene hydrate there is unquestionably less bleeding, but on the other hand quite a number of these patients were operated on with the region under local anesthesia. The reduction in the size of the bone flap has unquestionably reduced both the number and the size of hematomas.

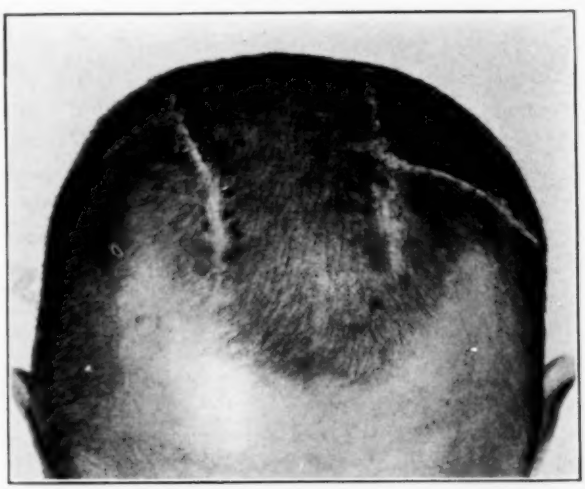

Fig. 7.—Operative scars left by surgical removal of bilateral subdural hematomas. The reduced size of the bone flap minimizes the operative risk so that both sides may be treated in a single operation.

When patients are very ill from the effects of intracranial pressure there is always the thought that it would be safer to remove the bone flap—now a small one—and play safe with life. Moreover, a postoperative hematoma would rarely form after removal of a flap. However, for cosmetic reasons, we have never done this at the primary operation because of a feeling of security as to the prompt detection of a hematoma. However, it has been necessary in several instances to remove the flap at the subsequent operation when a further risk of life was unjustifiable.

That postoperative bleeding is a serious argument against a cranioplastic operation and in favor of tapping and irrigating a hematoma cannot be denied. However, with the very low mortality in the series

the argument loses most of its force. If the patient is carefully watched there is scarcely any justification for loss of life. Then, too, when one considers the fact that the primary lesion is frequently multiple, it is clear that unless operation is performed the remaining pocket or pockets of blood may be missed, and in such circumstances a cure is scarcely to be expected. And of course tapping and irrigation offer no benefit for a patient with a solid hematoma.

Extradural drains were employed in 9 of the earlier cases (20 per cent) but were given up because of the risk of infection and because they contributed nothing to the prevention of hematoma.

When a subdural hematoma is present on both sides, the patient is placed in the so-called cerebellar position and the same procedure carried out on each side. Since the reduced size of the bone flap has cut the operative risk proportionately, both sides can be operated on with a single procedure (fig. 7).

RESULTS

Among the 48 patients there were 50 hematomas, the lesions of 2 patients being bilateral. Forty-six patients recovered and 2 died. The patient mortality therefore is 4.1 per cent; the case mortality, 4 per cent. The patient in case 27 had a wound infection and died of staphylococcic meningitis on the tenth day after the operation. Autopsy showed no other pathologic change. The patient in case 7 was in coma, with a temperature of 103.6 F., at the time of operation and died two days later. Autopsy in this case revealed nothing except edema of the brain. At the time of discharge from the hospital all the other patients were well. Subsequent reports from this group of patients have been gratifying. Twenty-eight are known to be in normal health in 1937, and among these are 2 who were operated on twenty years ago. No replies were received from 12 patients, and 6 are known to have died from causes unrelated to the hematoma a considerable time after their discharge from the hospital.

In summary, then, from this review of 48 cases one may conclude:

1. Subdural hematoma occurs with almost equal frequency in every decade of life.

2. Whereas trauma is probably the immediate cause of the hemorrhage, there may be some additional but unrecognized factor.

3. After the initial hemorrhage there can scarcely be any increase in size of the hematoma.

4. The diagnosis is difficult because unless the history of trauma is acceptable the clinical symptoms and findings do not differ from those produced by any intracranial space-occupying lesion.

5. In the cases in which trephining does not disclose the hematoma, adequate and at times precise localization can be made by ventriculographic study.

6. When a hematoma is suspected but not proved, a burr opening is made over the parietal region. Incision of the dura will establish or eliminate the diagnosis and determine the size and position of the bone flap.

7. A small craniotomy opening with evacuation of the hematoma is the operation of choice.

8. Postoperative bleeding has been of frequent occurrence. For very ill patients a decompression may occasionally be essential to recovery.

SURGICAL TREATMENT OF DIABETES MELLITUS

BILATERAL SECTION OF THE SPLANCHNIC NERVE AND DENERVATION OF THE LIVER

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In a communication before the Twelfth Congress of Physiology at Stockholm, Sweden, and in many subsequent papers, the Hungarian pharmacologist Mansfeld reported that he had observed a decrease of the blood sugar level after massive ligature of a part of the pancreas in which the circulation in the blood vessels was maintained. The decrease was more marked after two to three days of fasting (*Karenz-hypoglykämie*), and blood sugar curves after administration of dextrose indicated a better carbohydrate tolerance. On the basis of these findings, Linhardt and Hüttl [1] performed the operation in man with satisfactory results, which were later confirmed by de Takáts [2] and Wilder, who isolated with the thermocautery a piece of the pancreas of a 13 year old boy.

Thus the idea of a surgical cure of diabetes mellitus arose and gradually made progress. Returning to the argument today, I am sorry to say that the theoretic conceptions of the Hungarian pharmacologist have not led to any practical success. Opposition soon arose in the experimental field on the part of Ljvraga, Nather, Priesel and Wagner, Caccuri, Wohlgemuth, Seo and Mochizuki, Perrotti, Gahler, Ladurner and Unterrichter, Demel and Krammer and Falin,[3] who were

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1. Hüttl, T.: Versuche zur operativen Therapie des Diabetes, Orvósképzés **24**:7, 1934; Versuche zur operativen Behandlung der Zuckerkrankheit, Beitr. z. klin. Chir. **163**:206, 1936.

2. de Takáts, G.: Die chirurgische Beeinflussung des jugendlichen Diabetes, Arch. f. klin. Chir. **177**:242, 1933; Chirurgische Massnahmen zur Hebung der Zuckertoleranz, Klin. Wchnschr. **12**:623, 1933; Splanchnic Nerve Section in Juvenile Diabetes: II. Technic and Postoperative Management, Ann. Surg. **102**:22, 1935.

3. Falin, L.: Langerhanssche Inseln und Blutzucker nach Unterbindung der Ausführungsgänge der Bauchspeicheldrüse, Virchows Arch. f. path. Anat. **284**: 713, 1932.

followed in the clinical field by Pieri,[4] Hüttl and de Takáts,[2] who in a later paper recognized the error of the method he had previously followed.

This is fully justified by the results I have already published.[5] I stated that:

1. The isolation by ligature in mass of a part of a dog's pancreas from the duodenum, performed in such a manner that the connections through the blood vessels are maintained but pancreatic juice from the ligated part cannot flow into the intestine, is an operation which is well tolerated if of limited extent but poorly so if it is extensive.

2. Such an operation causes, after a while, atrophy of the acinous tissue, with a more marked sclerosis of the ligated tract, until it is reduced to a small cord of compact connective tissue, in which, however, the ganglions of the nerves and the pacinian corpuscles (in the cat) are conserved, a fact which proves the persistence of the blood supply. The islands of Langerhans do not show any special resistance, but they share the lot of the exocrine part of the organ, which sometimes presents involutional aspects resembling insular tissue.[6]

3. In the animal on which the operation is performed, the sugar content of the blood after a fast of twenty-four hours is much lower than in normal animals; after two to three days of fasting it becomes still lower. The increase in the sugar content of the blood after 1.75 Gm. of dextrose per kilogram of body weight has been given is usually less marked if the dextrose is given after not more than twenty-four hours of fasting, but it lasts longer, although it is often less marked, if the dextrose is given after two to three days of fasting. Only traces of insulin eliminated through the kidneys are found in the urine collected six to twelve hours after the last meal; insulin disappears completely after two to three days of fasting.

4. The character of the feces of the animals submitted to this operation, their loss of weight if adult and their failure to change in weight if young are signs of functional insufficiency of the external secretion of the ligated part of the pancreas.

5. The alterations which have been mentioned in the sugar content of the blood after fasting and after the carbohydrate tolerance test, the decrease and even disappearance of glycogen in the liver and the lower urinary elimination of insulin are proofs of functional insuf-

4. Pieri: Tentativi di cura chirurgica del diabete pancreatico, Soc. med.-chir. Bellunese, 1933, vol. 3.

5. Ljvraga, P.: Effetti della legatura massiva di una parte del pancreas, Arch. d. Ist. biochim. ital. **3**:391, 1931.

6. Ljvraga, P.: Innere und aüssere Sekretion der Drüsen, Arch. f. exper. Path. u. Pharmakol. **175**:572, 1934.

ficiency of the islands in the ligated part of the pancreas; therefore, there is a less active synthesis of glycogen from dextrose, while the opposite reaction is accelerated.

6. The suggestion by some authors of the ligature of a piece of the pancreas as a surgical treatment for diabetes does not seem to have any experimental basis, according to the data cited in this paper.

With the intention of furnishing the diseased organism a new tissue which would be able to function continuously and in harmony with the synergic organs, the so-called modified, sclerotic, atrophic or insular pancreas has been used in grafts. This modified organ was tested in animals by Jorns and Brancati. It is well known that the pancreas is particularly unsuitable for grafts, as it causes necrosis of the subcutaneous fatty tissue and necrobiosis of the adjoining tissues in other sites (Alessandri, Ottolenghi, Fichera). These modified glandular grafts seemed to have some real advantages. Unfortunately, even after seven to twelve months with completely fibrous organs some almost unimpaired lobules are not infrequently found (Ljvraga, Testa). After this lapse of time, if the complete harmlessness of the graft is to be assured, the insular tissue also must have been influenced by the newly created conditions to the extent that of the insular condition it retains only the name and the distribution in the midst of the intense sclerosis (Pende, Tiberti, Ukai, Wohlgemuth, Seo and Mochizuki, Caccuri, Ljvraga). It is then obvious that, even if this condition proves the atrophy of the ferment-producing tissue, on the other hand it hinders the nutritional exchanges between the graft and the surrounding tissues, thereby rendering difficult the setting of the transplant. In fact, it must be noticed that these grafts of modified pancreas have not had great success.

Experiments tending to find a basis for the surgical cure of diabetes were later performed by Goljanitzki, who studied in dogs the effects of the ligature of Stensen's duct on the sugar content of the blood and, encouraged by his results, together with Smirnowa [7] performed this operation on human subjects. In this procedure he was followed by Neuber, advised by Mansfeld, by Gohrbrandt, at the request of Seelig,[8] and by Angyan, Lucherini and Sussi. It may be stated, however, that the results were far from excellent.

In this connection, it may be said that I have been led into opposition to Goljanitzki, Parhon and Cahane, Urechia, Ciocanelli and Retezeanu, Dobrzaniecki and Michalowsky and Asano [9] by my experimental

7. Goljanitzki and Smirnowa: Weitere Erfahrungen mit der chirurgischen Behandlung des Diabetes, Ztschr. f. klin. Med. **105**:661, 1927.

8. Seelig, S.: Zur chirurgischen Behandlung der Zuckerkrankheit, Arch. f. klin. Chir. **157**:322, 1929.

9. Asano, Y.: Ueber die endokrine Funktion der Speicheldrüsen, Arch. f. jap. Chir. **12**:155, 213, 255 and 298, 1935.

controls of the histologic observations and by biochemical research on the salivary glands. Ligature of the salivary ducts or denervation or extirpation of the salivary glands, associated or not with partial or total pancreatectomy, led me to consider unfounded the view that there is an internal secretion, the study of which may have practical results leading to a surgical cure for diabetes. This opinion was later confirmed by the publications of Docimo.[10] Palma,[11] Glaser and Bannet,[12] Nishiyama,[13] Zimmerman and Soskin [14] and Simonetta.[14a]

All surgical intervention which tended toward hormonal substitution as a cure for diabetes having proved unsuccessful, another series of surgical corrections from a hormonal standpoint was attempted, based on present knowledge of the relations between the pancreas and other antagonistic glands, the thyroid, pituitary and adrenal, according to the well known table by Eppinger, Falta and Rudinger.

Friedmann and Gottesmann studied the effects of the ligature of the thyroid arteries; Allen studied the effects of the more or less extensive ablation of the gland. Rudy, Blumgart and Berlin (1935) [15] observed clinically the advantages of thyroidectomy in diabetes; Wilder, Foster and Pemberton (1934) [16] noted an improvement coincident with the appearance of a myxedematous condition. The administration of thyroid caused a return to the previous condition.

As to the pituitary gland, Houssay, Biasotti and co-workers had stated that in dogs deprived of it the extirpation of the pancreas does not cause a rise in the sugar content of the blood or dextrose in the

10. Docimo, L.: Gli effetti della legatura dei dotti di Stenone e della irradiazione della parotide sul metabolismo idrocarbonato, Gior. di clin. med. **14**: 510, 1933.

11. Palma, R.: Legatura dei dotti di Stenone e asportazione del pancreas, Riv. di pat. sper. **6**:419, 1931.

12. Glaser, E., and Bannet, I.: Wirken die Speicheldrüsen auf den Kohlehydratstoffwechsel inkretorisch ein? Klin. Wchnschr. **12**:345, 1933.

13. Nishiyama, Y.: Beitrag zur Kenntnis der Entwicklung der Glandula submaxillaris beim Kaninchen, nebst Bemerkungen über die Entstehung der sogenannten Bermann'schen Drüsen, Keijo J. Med. **3**:74, 1932.

14. Zimmerman, L. M.: Effect of Ligation of the Parotid Ducts on the Carbohydrate Tolerance of Normal Dogs, Arch. Int. Med. **49**:409 (March) 1932. Zimmerman, L. M., and Soskin, S.: Effect of Ligation of the Parotid Duct on the Carbohydrate Metabolism of Totally Depancreatized Dogs, ibid. **49**:663 (April) 1932.

14a. Simonetta, B.: Lo stato attuale delle nostre conoscenze intorno alla supposta secrezione interna delle ghiandole salivari, Athena **7**:74, 1938.

15. Rudy, A.; Blumgart, H. L., and Berlin, D. D.: Carbohydrate Metabolism in Human Hypothyroidism Induced by Total Thyroidectomy: III. A Case of Diabetes Mellitus Treated by Total Ablation of the Normal Thyroid Gland, Am. J. M. Sc. **190**:51, 1935.

16. Wilder, R. M.; Foster, R. F., and Pemberton, J. de J.: Total Thyroidectomy in Diabetes Mellitus, Endocrinology **18**:455, 1934.

urine. Davis [17] in his experimental research confirmed the findings of the South American authors. Considering the possibility of nervous influences—let me mention the *diabête tubérien* of Camus, Gournay and Le Grand (1925) [18]—Davis proved that if lesions are induced by the Horsley-Clarke apparatus in two localized symmetric points on the sides of the tuber cinereum, a little laterally with respect to the mamillary bodies, pancreatectomy will not cause diabetes. Chabanier, Puech, Lobo-Onell and Lélu [19] related some success in treating a diabetic condition in a 31 year old woman by the extirpation of the anterior lobe of the normal hypophysis. Thus they confirmed the results obtained by Hutton and Merle with the irradiation of the gland.

The adrenals also have been the object of surgical intervention in the treatment of diabetes in man. Ciminata,[20] in Baglioni's physiologic department, noticed that after bilateral denervation of the adrenals stimulation of the sciatic and other nerves with induced electric currents does not modify the sugar content of the blood or gives only a slight increase. He therefore stated that the intervention interrupts the reflex arc through which the increase in the sugar content of the blood is produced by means of epinephrine. The epinephrine contained in the denervated adrenals of cats deprived of the brain and spinal cord is less than normal, an observation which supports the statements of Tscheboksaroff, Stewart and Rogoff.[21] Ciminata deduced the possibility of influencing in this manner the sugar content of the blood in animals with experimental diabetes. The results of experiment confirmed this view and moreover proved that a positive adrenal factor is associated with a negative pancreatic factor, as Zuelzer had suggested.

The first denervation of the adrenals for human diabetes was performed by Donati in 1929.[22] The patient, a 57 year old woman, six

17. Davis, L.: The Relation of the Hypophysis, Hypothalamus and the Autonomic Nervous System to the Carbohydrate Metabolism, Ann. Surg. **100**: 654, 1934.

18. Camus, J.; Gournay, J. J., and Le Grand, A.: Diabète sucré par lésion nerveuse, Presse méd. **33**:249, 1925.

19. Chabanier, H.; Puech, P.; Lobo-Onell, C., and Lélu, E.: Hypophyse et diabète (à propos de l'ablation d'une hypophyse normale dans un cas de diabète grave), Presse méd. **44**:986, 1936.

20. Ciminata, A.: Guarigione del diabete pancreatico sperimentale, con l'enervazione operatoria delle glandule surrenali, Arch. di pat. e clin. med. **8**: 79, 1929.

21. Rogoff, J. M.: Addison's Disease Following Adrenal Denervation in a Case of Diabetes Mellitus, J. A. M. A. **106**:279 (Jan. 25) 1936.

22. Donati, M.: Le problème du diabète au pointe de vue chirurgical, Lyon chir. **31**:133, 1934; Tentativo di trattamento chirurgico del diabete con la enervazione di una capsula surrenale, Gior. d. r. Accad. di med. di Torino **92**: 463, 1929.

months before the operation had noted the first symptoms of fairly severe diabetes. The intervention, by means of a dorsolumbar incision, was unilateral (left) and was followed by marked improvement, which, however, was found three years later not to have persisted completely. Similar cases have been reported by Corachan and Simarro (1930) [23] and by Schmidt (1932). Finally Giordano [24] performed the denervation bilaterally, with two separate interventions, one on each side, in 2 diabetic patients with favorable results on the metabolism of carbohydrates. The diabetic gangrene presented by 1 of the patients, however, was not influenced. Therefore, the opinion expressed by Oppel, that unilateral adrenalectomy should be used preferably in cases of diabetes with gangrene of the extremities does not seem acceptable. Experimental controls on animals, however, proved that this intervention was unable to modify the course of apancreatic diabetes (Catan and Mazzocco, Turcatti, Viale, Carrasco Formiguera and Puche,[25] Hill and Koehler,[26] Labois and Ljvraga).

As the conclusion of my research, it was stated that acute diabetes caused by total pancreatectomy and milder forms caused by partial pancreatectomy were not favorably influenced by any intervention tending to diminish the secretion of epinephrine. Moreover, it was stated, in agreement with Pende, that denervation of the adrenals leads to complete atrophy of the medullary part, of which there remains a knot of substituted connective tissue, full of chalky depositions. Similar results were observed after the medullary part of the adrenals was removed with a sharp curet. Other authors have confirmed my conclusions; among them are de Takáts [2] and Gondard,[27] the latter from the institute of physiology directed by Hédon, who agrees with Nothmann in stating that Ciminata's results are to be attributed to imperfection in his method of extirpating the adrenals.

Perotti and Caprì,[28] deeming that the denervation of the adrenals is a difficult intervention to execute in man, studied the effects of partial

23. Corachan, M.: L'énervation des surrénals dans le traitement du diabéte, Trav. et mém. Cong. Soc. franç. chir., 1934, p. 898. Corachan, M., and Simarro, J.: Un caso de diabetes mellitus tratado con resultado favorable par la enervación operatoria de una glándula suprarrenal, Rev. méd. de Barcelona **14**:114, 1930; Arch. franco-belges de chir., 1934, p. 901.

24. Giordano: Deficienze circolatorie e gangrene dei piedi, Rassegna clin sc. **1**:403, 1933.

25. Carrasco Formiguera, R., and Puche, J.: Enervation des surrénales et diabète expérimental, Compt. rend. Soc. de biol. **108**:27 and 171, 1931.

26. Hill, E., and Koehler, A. E.: Effect of Suprarenalectomy on Sugar Tolerance, Proc. Soc. Exper. Biol. & Med. **30**:244, 1932.

27. Gondard, L.: Diabète et capsules surrénales. Résultats expérimentaux de la suppression de l'activité médullaire, Arch. internat. de physiol. **36**:329, 1933.

28. Caprì: Comportamento del diabete sperimentale dopo surrenectomia parziale, Boll. Soc. ital. di biol. sper. **8**:436, 1933.

adrenalectomy on the course of apancreatic diabetes. A series of unilateral adrenalectomies, which had been performed in man for various therapeutic reasons, showed that the intervention is well tolerated, the remaining adrenal having proved itself able to assume the function of both. The moderate improvement obtained was, however, temporary, as was to be expected, the effects of the intervention being nullified by the hyperplasia of the remaining adrenal tissue. On the other hand, Racchiusa and Criserà observed that in dogs from which the medullary adrenal tissue and in some cases most of the cortical tissue also had been removed not only was there no lowering of the sugar content of the blood but in several cases there was a tendency toward hyperglycemia as shown by the dextrose tolerance test.

In man too, Sussig brought about no improvement by intervention of this type in a case of diabetes in a child in which ligature of the salivary (Stensen's) duct had previously been performed without noticeable results. Pieri,[4] having observed that after extirpation of the left adrenal gland in a case of hypertension the blood sugar diminished, was led to perform the same intervention in a 23 year old diabetic patient. This case is of little value as evidence, however, since the patient died five months later.

The sympathetic nervous system also has been the object of much research in attempts to find a practical surgical cure for diabetes. Rupp observed hypersensibility to insulin after section of the splanchnic nerves, and Stelling observed a diminution in the sugar content of the blood for some hours after anesthesia of these nerves in 77 per cent of his cases of diabetes. These results led de Takáts and Cuthbert [29] to study the effects of bilateral splanchnicotomy on the sugar content of the blood in dogs. These authors observed a better carbohydrate tolerance, a phenomenon which had likewise been observed after denervation of the adrenals. Subsequently de Takáts and his co-workers Fenn and Trump [30] performed splanchnicotomy in man by a method similar to that described by Pieri,[4] who stressed that this intervention should be applied in cases of diabetes in children who are resistant to insulin and sensitive to ergotamine. The operation, performed on a 13 year old girl, lowered the daily requirement of insulin from 40 to 20 units. The authors concluded that the girl remained diabetic as before, although more sensitive toward insulin; this conclusion does not seem encouraging. Nevertheless, de Takáts affirmed, not without reason,

29. de Takáts, G., and Cuthbert, E. P.: Effect of Suprarenal Denervation and Splanchnic Section on the Sugar Tolerance of Dogs, Arch. Surg. **30**:151 (Jan.) 1935.

30. de Takáts, G., and Fenn, G. K.: Bilateral Splanchnic Nerve Section in a Juvenile Diabetic, Ann. Int. Med. **7**:422, 1933. de Takáts, G.; Fenn, G. K., and Trump, R. A.: Splanchnic Nerve Section in Juvenile Diabetes: I. Selection of Cases for Operation, Ann. Int. Med. **7**:1201, 1934.

that apancreatic diabetes in dogs is only partially comparable to human diabetes and that the intervention should be attempted only in the treatment of diabetes in children, which represents the genuine form of the disease, and he stressed the importance of this intervention. He moreover reported other cases, in 1 of which the daily requirement of insulin was reduced from 50 to 5 units.

Donati, before the Society of Surgery of Lombardy (Italy), reported a splanchnicectomy on the left side (Pende's operation) in a case of hypertension (nondiabetic) after which no changes in the sugar content of the blood were noted. On the other hand, Stropeni [31] reported that in 1 of 2 cases of angiotrophoneurosis treated by cutting the splanchnic nerves the blood sugar diminished from 130 to 90 mg. per hundred cubic centimeters. Ciceri and Gabrielli [32] performed anesthesia or alcoholic treatment of the splanchnic nerves in both diabetic and nondiabetic persons; besides a fall in the blood pressure, they observed an early, rapid and marked drop in the blood sugar curve, indicating better carbohydrate tolerance.

In the experimental field Puche reported that he noted no decrease in the blood sugar after splanchnicotomy in normal dogs. De Takáts [33] studied also the effects of the extirpation of the celiac ganglion in animals. He stated that this intervention brings about a marked increase in carbohydrate tolerance and hypersensibility to insulin. Apparently he had not taken into consideration the effects, observed by Marassini and many others, that such an intervention has on the abdominal organs. Spadolini recently called attention to the dangers of such an operation. Other authors turned their attention toward one of the organs more directly concerned with the metabolism of carbohydrates, the liver, the capital importance of which was proved by C. Bernard's studies on glycogenesis and received new light from Mann and Magth's experiments in hepatectomy.

Depisch, Hasenöhrl and Schönbauer,[34] of Falta's school, performed the denervation of the hilus of the liver in normal animals and in ani-

31. Stropeni, L.: La sezione dei nervi splancnici (operazione di Pende) nella cura della arteriopatie spastiche, Boll. e mem. Soc. piemontese di chir. **4**:1184, 1934.

32. Ciceri, C., and Gabrielli, S.: Effetti immediati e lontani sulla curva glicemica e sulla pressione arteriosa della enervazione monolaterale e bilaterale delle surrenali, Ann. ital. di chir. **13**:417, 1934; Studi sulle variazioni della glicemia alimentare indotte dalla alcoolizzazione degli splancnici: Tentativi di cura del diabete mellito, ibid. **38**:121, 1934.

33. de Takáts, G., and Cuthbert, F. P.: Effect of Coeliac Ganglionectomy on the Sugar Tolerance of Dogs, Am. J. Physiol. **102**:614, 1932.

34. Depisch, F.; Hasenöhrl, R., and Schönbauer, L.: (*a*) Ueber die operative Beeinflussung des Zuckerstoffwechsels; die Durchsneidung der vegetativen Nerven im ligamentum hepatoduodenale beim normalen Hund, Klin. Wchnschr. **9**:1437, 1930; (*b*) Wien. klin. Wchnschr. **43**:125, 1930.

mals with mild experimental diabetes; a marked decrease in the blood sugar curves after administration of dextrose was observed, indicating a better carbohydrate tolerance. In 1 dog, however, with severe diabetes from subtotal ablation of the pancreas, no favorable influence was exerted by the intervention. It must be recalled here that Christie, Macleod and Pearce [35] had previously reported observing after stimulation of the hepatic plexus effects similar to those produced by puncture of the fourth ventricle. Kaufmann, however, sustained the view that total denervation of the liver does not modify the regulation of blood sugar in animals deprived of the pancreas, although it lowers the blood sugar in normal animals. Leone [36] observed a temporary alteration in the biligenic and glycogenic functions of the liver in dogs after sympathectomy of the hepatic artery. Chianello [37] reported after the same intervention a considerable congestion of the liver and a constant and gradual decrease in the sugar content of the blood during a period of thirty to fifty-six days, after which time the circulation of the blood was restored. On the contrary, sympathectomy of the portal vein caused the blood sugar to increase definitely for one month and then to fall below the preoperative level.

De Fermo [38] reported low blood sugar readings with the lowest between the tenth and the twentieth day after intervention, and a lowering of the dextrose tolerance curves for a period of one to two months. Komatsu [39] reported a better tolerance of carbohydrates introduced per os after sectioning all the nerve filaments contained in the hepatoduodenal ligament. The higher apex and the later return to the initial readings of the dextrose tolerance curve after partial extirpation of the pancreas fell to normal or nearly normal readings after denervation of the liver. Denervation was performed from two and a half to four months after the first intervention in cases of rather mild diabetic conditions (one eighth to one fourth of the pancreas left). The denervation of the liver associated with simultaneous partial pancreatectomy,

35. Macleod, J. J. R., and Pearce, R. G.: The Relationship of the Adrenal Glands to Sugar Production by the Liver, Am. J. Physiol. **29**:419, 1911-1912.

36. Leone, P.: La simpaticectomia dell'arteria epatica in rapporto ai processi riparativi ed alle funzione biligenica e glicogenica del fegato, Arch. ital. di chir. **18**:346, 1927.

37. Chianello, C.: La simpatectomia della vena porta, Ann. ital. di chir. **9**: 343, 1930; Modificazioni istologiche del fegato ed influenza sulla glicemia in seguito alla simpaticectomia dell' arteria epatica, Cultura med. mod. **6**:411, 1927; La simpatectomia dell' arteria epatica, ibid. **8**:289, 1929.

38. de Fermo, C.: Studi sperimentali sulla simpaticectomia perivasale. Esame funzionale del fegato nella simpaticectomia dell'arteria epatica, Arch. ital. di chir. **28**:381, 1931.

39. Komatsu, Y.: Ueber die operative Beeinflussung des Zuckerstoffwechsels, Arch. f. klin. Chir. **174**:65, 1932.

even with mild diabetes, was followed by a smaller increase in the blood sugar after administration of dextrose and by a more noticeable hypoglycemia after meals. Epinephrine, which usually causes a greater increase in the blood sugar in diabetic dogs than in normal dogs, caused no variations in either group.

Donald [40] and de Takáts,[29] on the other hand, observed no influence from denervation of the liver on the carbohydrate tolerance. This agrees with Kaufmann's findings, already mentioned, and with those cited by Palmer [41] in his monograph on hepatolytic intoxication. In the clinical field, Hirschhorn and Popper [42] observed after paravertebral anesthetic block of the eighth, ninth and tenth right dorsal nerves a smaller increase of the blood sugar after meals, hypersensibility to insulin and absence of the increase of the blood sugar caused by epinephrine. The blood sugar, which remained unchanged in normal persons, was often markedly lowered in persons with diabetes. Finally, let me mention the experimental work with ergotamine done by Moretti, Bufano, Cesa-Bianchi, Franco, Pollak and Selinger, Rothlin and others. These authors observed in diabetic patients that this drug, alone or associated with atropine, lowered the sugar content of the blood.

EXPERIMENTS IN SPLANCHNICOTOMY AND DENERVATION OF THE HILUS OF THE LIVER

After the series of experiments I had already undertaken for the purpose of studying the possibility of a surgical cure for diabetes, which I have mentioned, I undertook a complementary study of the effects of splanchnicotomy and denervation of the hilus of the liver on the blood sugar in normal animals and in animals with experimental diabetes. The former of these interventions has been performed on man because of various clinical indications (by Durante,[43] Craig and Brown, Donati,[22] Pieri,[4] Stropeni [31] and others), and the latter seemed to me an intervention which would not be difficult to apply clinically.

For the determination of the blood sugar I used the Folin-Wu method. This method gives slightly higher figures than the Bang and the Hagedorn-Jensen method, but it has been preferred in laboratory

40. Donald, J. M.: Studies on Carbohydrate Metabolism Following Denervation of the Liver, Am. J. Physiol. **98**:605, 1931.

41. Palmer, R. G.: Physiopathologie des opérations sur le foie et les vaisseux hépatiques, Paris, E. Le François, 1934.

42. Hirschhorn, S., and Popper, H. L.: Ueber den Einfluss der paravertebralen Injektion auf Vorgänge der Stoffwechselregulation, Wien. klin. Wchnschr. **46**: 365, 1933. Popper, H. L., and Hirschhorn, S.: Die Beeinflussung der Galaktoseausscheidung durch paravertebrale Injektion, ibid. **45**:268, 1932.

43. Durante, L.: La midollectomia surrenale isolata ed associata alla resezione dei nervi splancnici, J. internat. de chir. **1**:579, 1936.

tests because of the greater constancy of the results for comparative purposes. The animals used were 18 dogs; they were all stray dogs and in poor general condition. For this reason they were first kept several days at rest to improve their state of nutrition.

The diet before and after intervention was an ordinary uniform mixed diet.

TABLE 1.—*Effects of the Denervation of the Stem of the Liver*

Experiment No.	Animal No.	Date	Grams of Dextrose in 1,000 Cc. of Blood				
			Before Administration of Dextrose	After Administration of 1.75 Gm. of Dextrose per Kilogram of Body Weight			
				½ Hr.	1 Hr.	2 Hr.	3 Hr.
1	1	5/18/32	0.89	1.34	1.19	1.07	0.80
2	1	5/21/32	1.01	1.55	1.23	1.00	0.76
		6/20/32	Denervation of the stem of the liver				
3	1	7/ 5/32	0.86	1.14	1.05	0.79	0.83
4	1	7/21/32	0.90	1.11	1.07	0.88	0.76
5	1	8/ 5/32	0.73	1.19	1.02	0.75	0.81
6	1	8/20/32	0.83	0.86	0.79	0.76	0.81
7	1	9/30/32	0.89	1.25	1.14	1.01	0.87
9	2	5/24/32	1.05	1.32	1.19	0.86	0.83
10	2	5/26/32	0.94	1.38	1.13	0.93	0.88
		6/20/32	Denervation of the stem of the liver				
11	2	7/ 6/32	0.96	1.22	1.09	0.99	0.89
12	2	7/20/32	0.79	1.16	1.07	0.86	0.82
13	2	8/ 6/32	0.80	1.05	1.02	0.91	0.83
14	2	8/21/32	0.90	1.20	1.17	0.83	0.81
15	2	9/21/32	0.98	1.33	1.13	0.75	0.80
16	3	5/19/32	0.86	1.27	1.10	1.03	0.70
17	3	5/29/32	0.91	1.25	1.14	0.95	0.83
		6/14/32	Denervation of the stem of the liver				
18	3	6/30/32	0.83	1.17	1.08	0.85	0.88
19	3	7/15/32	0.86	1.08	1.08	1.06	0.90
20	3	8/15/32	0.76	0.98	0.90	0.87	0.84
21	3	9/29/32	0.94	1.18	1.13	0.91	0.88
22	3	10/20/32	0.98	1.42	1.29	1.03	0.92
23	4	5/23/32	1.07	1.43	1.26	1.11	1.02
24	4	5/31/32	0.96	1.53	1.29	1.07	0.86
		6/14/32	Denervation of the stem of the liver				
25	4	7/10/32	0.94	1.25	1.16	1.03	0.98
26	4	8/16/32	0.93	1.18	0.86	0.88	0.85
27	4	8/23/32	0.87	1.03	1.04	0.78	0.76
28	4	9/28/32	0.81	1.28	1.14	1.07	0.81
29	4	10/22/32	0.93	1.50	1.33	1.19	1.00

The blood sugar after twenty-four hours of fasting and the curves after introduction through a Rehfuss tube of 1.75 Gm. of dextrose, dissolved in 2.5 cc. of water per kilogram of body weight, were repeatedly examined. Samples of blood were taken from the saphenous vein before the administration of dextrose and one half, one, two and three hours after the administration. The dog was left loose so that the rise in the blood sugar from fetters (*Fesselungshyperglykämie*) would not interfere with the results. At the necropsy pieces were taken from several organs for histologic examination.

TABLE 2.—*Effects of Partial and Complete Pancreatectomy and Denervation of the Stem of the Liver*

Experiment No.	Animal No.	Date	Grams of Dextrose in 1,000 Cc. of Blood: Before Administration of Dextrose	After Administration of Dextrose: ½ Hr.	1 Hr.	2 Hr.	3 Hr.	Glycosuria, %	Kg.
29	5	5/20/32	0.90	1.23	1.11	0.94	0.84	....	13.5
		5/22/32	Partial pancreatectomy (25.3 Gm.)						
30	5	6/ 6/32	1.67	1.92	2.50	2.95	2.38	3.8	11.5
31	5	6/22/32	1.96	2.10	2.92	2.14	2.40	4.6	11
32	5	7/24/32	2.14	2.39	2.52	3.43	2.78	5	10.3
		7/25/32	Denervation of the stem of the liver						
33	5	8/10/32	1.78	2.09	2.38	2.39	2.05	5	9.5
34	5	8/26/32	2.06	2.61	2.67	2.63	1.92	4.4	9.7
35	5	9/24/32	2.31	2.62	3.07	2.78	2.57	5.7	9.3
		10/ 2/32	Extirpation of the transplanted part of the pancreas (4.6 Gm.)						
36	5	10/ 2/32	3.43	4.88	5.20	4.52	3.85	13	9.4
37	5	10/ 3/32	3.78						
38	5	10/ 4/32	3.27	....	....	....	....	8.7	9.1
39	6	5/17/32	0.92	1.29	1.17	0.85	0.77	....	12
40	6	5/28/32	0.89	1.31	1.01	0.74	0.78	....	12
		6/ 2/32	Partial pancreatectomy (18 Gm.)						
41	6	6/21/32	1.25	1.61	2.19	2.06	1.35	1.15	11.5
42	6	7/29/32	1.34	2.05	2.28	1.90	1.29	....	....
43	6	8/ 1/32	1.36	1.94	2.09	1.64	1.33	1.37	10.9
44	6	9/ 1/32	1.49	2.09	2.33	1.55	1.30	1.90	10.5
		9/ 6/32	Denervation of the stem of the liver						
45	6	9/21/32	1.10	1.69	1.69	1.47	1.21	1.07	10.7
46	6	10/ 6/32	1.24	1.48	1.73	1.31	1.16	2	9.8
47	6	10/21/32	0.92	1.06	1.12	1.05	1.05	0.97	10.2
48	6	11/ 6/32	1.10	1.23	1.48	1.38	1.25	2.6	10.3
49	6	12/ 6/32	1.21	1.55	1.40	1.22	1.24	1.7	9.9
		12/ 9/32	Extirpation of the transplanted part of the pancreas (9.4 Gm.)						
50	6	12/10/32	4.5	....	....	....	....	5.6	9.5
51	6	12/11/32	4.1	....	....	....	....	6	9.7
52	7	5/15/32	0.96	1.56	1.20	0.94	0.87	....	14.5
53	7	5/30/32	0.99	1.31	1.13	0.94	0.79	....	14.5
		6/ 2/32	Partial pancreatectomy (29 Gm.)						
54	7	6/23/32	1.10	1.57	1.61	1.49	1.15	0.56	14
55	7	7/ 3/32	1.12	1.47	1.69	1.38	1.16	1.21	13.7
56	7	7/18/32	1.24	1.90	1.66	1.30	1.34	2.3	13.5
57	7	8/ 1/32	1.49	2.05	1.98	1.61	1.62	2.91	12.8
58	7	9/ 7/32	1.50	1.51	2.09	1.78	1.46	1.77	13.2
59	7	10/ 4/32	1.38	1.66	1.78	1.47	1.20	1.33	13
		10/ 8/32	Denervation of the stem of the liver						
60	7	10/23/32	1.00	1.31	1.24	1.06	1.07	0.71	12.7
61	7	11/ 8/32	1.05	1.16	1.19	1.15	1.06	0.77	13.1
62	7	11/23/32	0.92	1.08	0.98	0.80	0.95	0.33	13
63	7	12/ 7/32	1.28	1.34	1.63	1.61	1.21	3	12.5
64	7	12/22/32	1.22	1.37	1.88	1.42	1.28	2.43	12.3
65	7	1/ 7/33	1.45	1.47	1.73	1.65	1.37	1.90	12.6
		1/ 7/33	Extirpation of the transplanted part of the pancreas (10 Gm.)						
66	7	1/ 8/33	2.77	3.55	3.89	4.00	2.90	9	12
67	7	1/ 9/33	4.10	5.55	5.79	4.37	3.69	16	11.6
68	7	1/12/33	3.78	....	....	....	....	11	11.1
69	8	5/25/32	1.01	1.58	1.15	1.03	0.91	....	9.5
70	8	5/27/32	1.06	1.42	1.05	1.07	0.88	....	9.5
		6/ 8/32	Partial pancreatectomy (11 Gm.)						
71	8	6/21/32	1.38	1.73	2.10	1.46	1.43	2.13	9
72	8	7/ 7/32	1.91	2.95	3.06	2.70	2.06	3.20	9.1
73	8	7/23/32	2.21	2.52	3.25	2.00	2.12	3.55	8.6
74	8	8/ 7/32	2.11	2.85	2.95	2.35	1.98	1.94	8.7
75	8	8/22/32	1.60	3.00	3.01	3.09	1.90	4	8.4
76	8	9/10/32	2.06	2.53	2.93	2.11	2.11	5.90	8.2
		10/11/32	Denervation of the stem of the liver						
77	8	10/23/32	1.24	1.19	1.12	1.21	1.24	3.1	8
78	8	10/10/32	1.17	1.48	1.22	1.15	1.13	2.25	8.3
79	8	10/25/32	1.34	1.38	1.28	1.17	1.20	2.10	8.5
80	8	11/10/32	1.43	1.57	2.18	1.77	1.49	3.22	8.3
81	8	12/10/32	1.57	2.09	3.05	2.02	1.78	4.00	8.7
82	8	1/10/33	1.40	1.66	2.06	1.33	1.35	2.60	8.6
		1/13/33	Extirpation of the transplanted part of the pancreas (14 Gm.)						
83	8	1/14/33	2.90	2.99	3.44	4.50	3.00	10	8.4
84	8	1/16/33	4.23	....	....	....	....	13	7.9

TABLE 2.—*Effects of Partial and Complete Pancreatectomy and Denervation of the Stem of the Liver—Continued*

Experiment No.	Animal No.	Date	Grams of Dextrose in 1,000 Cc. of Blood: Before Administration of Dextrose	After Administration of Dextrose: ½ Hr.	1 Hr.	2 Hr.	3 Hr.	Glycosuria, %	Kg.
85	9	5/31/32	1.02	1.60	1.19	0.92	0.85	....	19
86	9	6/ 4/32	0.86	1.55	1.07	1.01	0.91	....	19
		6/ 8/32	Partial pancreatectomy (34 Gm.)						
87	9	6/23/32	1.48	2.50	1.83	1.62	1.51	....	....
88	9	7/ 7/32	1.37	1.98	1.90	2.13	1.71	1.87	18
89	9	7/24/32	1.78	2.65	2.35	1.69	1.84	3.10	17.8
90	9	8/12/32	1.96	2.91	2.85	2.39	2.00	4.30	17
		9/ 8/32	Denervation of the stem of the liver						
91	9	9/28/32	1.35	1.57	1.34	1.40	1.39	2.70	16.6
92	9	10/14/32	1.31	1.95	1.50	1.27	1.25	....	....
93	9	11/29/32	1.21	1.25	1.59	1.30	1.16	3.15	17
94	9	12/12/32	1.47	1.69	1.47	1.38	1.34	3	17
95	9	1/12/33	2.05	2.63	2.28	1.90	1.60	5.60	16.3
96	9	1/17/33	1.76	2.39	2.07	1.79	1.68	4.30	16
		1/17/33	Extirpation of the transplanted part of the pancreas (11.7 Gm.)						
97	9	1/18/33	2.77	2.94	5.10	2.56	2.69	7	16
98	9	1/19/33	3.13	3.57	4.40	3.33	3.21	9	15.7
99	9	1/20/33	3.57	....	....	....	....	13	
100	9	1/20/33	3.11	....	....	....	....	6.50	15.3

General anesthesia was induced by morphine and ether. An incision just below and parallel to the right costal arch was made. After the abdominal cavity was opened, the stem of the liver was sought. The surgeon's left index finger was introduced into the foramen of Winslow; the hepatoduodenal ligament was then lifted and well exposed.

All the nerve filaments which run in or are interwoven over the hepatic arteries (after detachment of the gastroduodenal from the hepatoduodenal artery, to prevent interference with the pancreatic nerves) and all nerve filaments interwoven over the bile ducts and the principal portal vein were then accurately isolated and severed high up toward the liver. Moreover, for greater surety Doppler's isophenol (6 per cent phenol to which isomers of tricresol are added to neutralize its caustic action) was applied locally for about 2 cm. with a brush.

As may be seen in table 1, the blood sugar was not much lowered by denervation of the stem of the liver. I should say rather that it varies within the normal limits, although for some time (about three months) there is a tendency to settle near the minimum normal figures. According to many authors the normal readings in dogs are between 1.06 and 0.73 per cent (Macleod, Morgulis, Oppler and Rona, Pi Suñer and Puche and Houssay and co-workers).

When the blood sugar curves after administration of dextrose were plotted, a smaller rise and in some cases a marked end fall of the curve was observed (the posthyperglycemic hypoglycemia described by Depisch, Hasenöhrl, Rubino and Varela). In dog 1 a paradoxic curve was obtained three months after intervention. These findings, which however after four months diminished, the sugar content of the blood returning to, or even becoming higher than, preoperative values (e. g., in animal 4), were explained as signs of better carbohydrate tolerance.

PARTIAL AND COMPLETE EXTIRPATION OF THE PANCREAS

In another series of experiments I performed partial extirpation of the pancreas (about four fifths), cutting away the part which is supplied by the pancreaticoduodenal artery and by the splenic branches. The part supplied by the mesenteric blood vessels, which is easily recognizable because it retains its pinkish color while the rest is cold and cyanotic, was transplanted under the skin according to Hédon's method. The skin was protected with collargol ointment and cleaned with a dilute solution of hydrochloric acid. After recovery from the intervention, the course of the mild experimental diabetes was determined, and the effects of the denervation of the stem of the liver were studied two months later. Finally the transplanted part of the pancreas was taken away, so that the reactions could be studied in the same dog deprived completely of the pancreas. The results may be seen in table 2.

From the results of the dextrose tolerance test (table 2) it is evident that the partial extirpation of the pancreas caused in all cases a more or less marked diabetes, as was shown by the change in the general condition, by the hyperglycemia and by the presence of sugar in the urine (Benedict's test).

After denervation of the stem of the liver the apex of the blood sugar curve was lowered more or less; this was especially evident in dog 6. In some cases the figures of the single readings on the plotted curve are placed on a slightly jagged line, as in the case of dog 5 one month after the intervention and dog 6 one and a half months after the intervention. The initial readings for the blood sugar after fasting about one month after the intervention are also generally lower, and the final readings sometimes show a tendency toward posthyperglycemic hypoglycemia. In the case of dog 5, in which the partial extirpation of the pancreas was followed by a severe form of diabetes, the denervation of the stem of the liver had no favorable effects. The behavior of the alimentary hyperglycemia shows that the advantages obtained in the other cases were temporary, with a tendency to disappear in about three months and return to preoperative conditions; the intervention, moreover, did not modify the rapidly fatal course that is usually observed after extirpation of the graft of the remaining pancreatic tissue.

BILATERAL SPLANCHNICOTOMY

In a third series of experiments I investigated the effects of splanchnicotomy on the blood sugar. With the animal under anesthesia induced with morphine and ether, a median laparotomy incision was made; the greater and lesser splanchnic nerves were brought into evidence by the technic I have described in a previous paper. The nerves were then passed over a large loop of silk; a piece about 1.5 cm. long

was cut away, and the cut ends were bent and fixed in opposite directions. This was done because of their tendency to regeneration which is so great that de Takáts,[2] for the same reason, sutured the upper cut end of the nerve to the tenth intercostal nerve. The results may be seen in table 3. The remarks made about the denervation of the liver may be here repeated; they agree with what I stated relative to the suppression of the epinephrine function.[44]

TABLE 3.—*Effects of Section of the Splanchnic Nerve*

			Grams of Dextrose in 1,000 Cc. of Blood				
				After Administration of 1.75 Gm. of Dextrose per Kilogram of Body Weight			
Experiment No.	Animal No.	Date	Before Administration of Dextrose	½ Hr.	1 Hr.	2 Hr.	3 Hr.
101	10	6/ 9/32	0.99	1.32	1.11	0.95	0.89
102	10	6/12/32	1.01	1.39	1.17	1.00	1.00
		6/19/32	Section of the splanchnic nerve				
103	10	7/ 1/32	0.81	1.23	1.13	1.01	0.86
104	10	7/19/32	0.75	1.15	1.11	0.91	0.93
105	10	8/ 3/32	0.67	1.19	1.10	1.00	0.91
106	10	8/19/32	0.87	1.23	1.09	1.07	0.99
107	10	9/19/32	1.05	1.26	1.07	1.05	0.88
108	10	10/18/32	1.00	1.33	1.19	0.87	0.87
110	11	6/11/32	0.95	1.51	1.13	0.97	0.97
111	11	6/13/32	1.00	1.47	1.19	1.00	1.02
		6/19/32	Section of the splanchnic nerve				
112	11	7/ 8/32	1.05	1.27	1.20	1.11	1.03
113	11	8/26/32	0.78	1.37	1.12	0.93	1.03
114	11	8/ 9/32	0.78	1.12	1.05	1.05	0.83
115	11	8/18/32	0.87	1.18	1.04	0.85	0.81
116	11	9/ 6/32	0.91	1.29	1.09	1.03	1.00
117	11	10/ 8/32	0.91	1.39	1.21	1.00	1.04
117	12	6/ 7/32	0.96	1.43	1.14	0.90	0.91
		6/25/32	Section of the splanchnic nerve				
118	12	7/11/32	0.80	1.23	1.07	0.94	0.89
119	12	7/27/32	0.87	1.25	1.05	0.98	0.86
120	12	8/11/32	0.64	1.15	1.11	1.00	0.79
121	12	8/29/32	0.80	1.10	1.09	1.03	0.68
122	12	9/11/32	0.79	1.29	1.17	1.03	0.87
123	12	10/11/32	1.00	1.38	1.22	1.00	1.03
123	13	6/15/32	0.96	1.45	1.21	0.88	0.87
124	13	6/18/32	Section of the splanchnic nerve				
125	13	7/ 9/32	0.81	1.21	1.10	0.96	0.88
126	13	7/28/32	0.78	1.20	1.05	0.95	0.86
127	13	8/13/32	0.83	1.22	1.08	0.93	0.91
128	13	8/30/32	0.60	1.17	1.09	1.00	0.88
129	13	9/13/32	0.85	1.26	1.14	0.93	0.95
130	13	10/13/32	0.87	1.39	1.20	0.98	0.83

The fasting blood sugar falls inconstantly below the minimum normal readings, but the hypoglycemia is not marked. The blood sugar curves after administration of dextrose in general remain lower than before intervention for about two months afterward but later show a marked tendency to return to normal values. In some cases there are but slight variations, so that the plotted curve is a straight or slightly wavy line.

44. Ljvraga, P.: Surrenali e diabete: Contributo alla fisiopatologia dei surreni, Riv. di pat. sper. **10**:107, 1933.

Administration of the dextrose tolerance test according to the method described facilitates the observation of results not only in cases of mild or chronic diabetes of the Sandmeyer type but in cases of the severe condition that takes place after extirpation of the rest of the organ. This test showed that the beneficial results in animals submitted to splanchnicotomy were not more marked than those in animals deprived of the medullary adrenal tissue or with denervated livers (table 4). This statement results from a comparison of tables 2 and 4 of this paper with those of a previous paper.[44]

In the postmortem examination of my experimental animals, a considerable degree of congestion of the liver was observed; the organ was enlarged and of rather soft consistency and dark red in color in 2 dogs killed two weeks after denervation of the stem of the liver. These observations were more marked in 2 other animals killed two weeks after splanchnicotomy. Histologic sections showed a thinning of the radial cellular columns among the enlarged capillaries full of blood around the central vein of the lobule, which was widely distended (figs. 1 and 2). The cells were smaller than is normal, and the kernels were more deeply colored by hematoxylin than usual. The protoplasm was dark, often with several round vacuoles, which were shown by specific staining methods to contain fat.

In slices stained by the Vastarini-Cresi method glycogen was observed in the central part of the lobules in the form of a few small grains; in determinations by Pflüger's method the glycogen content was shown to be less than 1 per cent. In dogs 5 and 14 to 18, necropsy was performed about three months after the denervation of the liver and the splanchnicotomy respectively. The observations described were less marked; there were, however, vascular congestion of the central and perilobular blood vessels and a fair quantity of fat in the cells of the liver with a relative scarceness of glycogen as revealed by the Vastarini-Cresi stain. Histologic sections of the stem of the liver, when stained by Cajal's method, showed a greater quantity of connective tissue and rare slender nerve fibers, generally attached to the portal vein. At necropsy on the dogs studied in tables 2 and 4, the liver was seen to be normal in size; fat was abundant and diffusely distributed in the hepatic cells, as shown by the scarlet red stain, and rare, small blocks of glycogen were present, especially in the central part of the lobule, as seen by the Vastarini-Cresi method, the quantity being 3.3 to 4.5 per cent as analyzed by Pflüger's method.

The adrenals of animals in which the stem of the liver was denervated showed only hyperemia, especially in the medullary part, two weeks after intervention; the structure was seen to be normal if examined in later periods. In dogs submitted to bilateral splanchnicotomy,

TABLE 4.—*Effect of Partial and Complete Pancreatectomy and Section of the Splanchnic Nerve*

Experiment No.	Animal No.	Date	Grams of Dextrose in 1,000 Cc. of blood: Before Administration of Dextrose	After Administration of Dextrose: ½ Hr.	1 Hr.	2 Hr.	3 Hr.	Glycosuria, %	Kg.
131	14	1/18/33	1.00	1.49	0.93	1.05	0.86	....	20
132	14	1/21/33	1.03	1.42	1.07	1.00	0.84	....	20
	14	1/28/33	Partial pancreatectomy (26 Gm.)						
133	14	2/12/33	1.50	1.73	1.55	1.37	1.44	2.30	18.9
134	14	2/22/33	1.62	2.19	2.31	2.05	1.90	....	....
135	14	3/23/33	2.11	2.00	2.01	2.00	2.10	3	19
	14	3/24/33	Section of the splanchnic nerve						
136	14	4/ 8/33	1.38	1.67	1.45	1.33	1.40	2.05	18.5
137	14	4/24/33	1.31	1.53	1.60	1.29	1.29	....	....
138	14	5/ 8/33	1.27	1.39	1.48	1.36	1.30	2.40	18.8
139	14	5/25/33	1.32	1.70	1.73	1.42	1.40	2	19
140	14	6/ 8/33	1.54	1.81	1.41	1.41	1.38	....	....
145	14	7/ 8/33	1.37	1.76	1.87	1.39	1.42	3.35	19.4
	14	7/ 9/33	Extirpation of the transplanted part of the pancreas (11 Gm.)						
146	14	7/ 9/33	2.53	3.23	3.70	2.42	2.60	7.45	19
147	14	7/11/33	3.70	4.51	5.10	5.00	4.20	12.50	18.7
147	15	1/19/33	0.95	1.38	1.07	0.93	0.93	....	13
148	15	1/22/33	0.98	1.39	0.99	0.90	0.91	....	13
	15	1/25/33	Partial pancreatectomy (19.7 Gm.)						
149	15	2/ 5/33	2.00	2.39	3.10	2.64	2.06	3.10	12.4
150	15	2/20/33	1.60	2.55	2.97	1.93	1.75	....	....
151	15	3/ 7/33	2.09	3.00	3.34	2.80	1.94	4.20	12
152	15	3/13/33	Section of the splanchnic nerve						
152	15	3/31/33	2.00	3.01	3.09	2.34	1.92	3.50	11.8
153	15	4/11/33	1.55	2.35	2.60	1.90	1.69	3.70	11.8
154	15	4/26/33	1.62	2.70	2.44	1.74	1.78	....	....
155	15	5/13/33	1.49	1.53	2.00	2.07	1.60	4	11.6
156	15	6/13/33	1.58	2.10	2.85	1.66	1.62	4.18	11.3
157	15	7/13/33	1.38	1.86	2.15	1.96	1.73	4.37	11.5
159	15	7/17/33	Extirpation of the transplanted part of the pancreas (9.5 Gm.)						
158	15	7/19/33	2.28						
159	15	7/21/33	3.34	4.00	4.70	4.18	3.57	15	11
160	15	7/21/33	4.55						
161	16	1/26/33	1.01	1.65	1.10	0.96	0.87	....	15
162	16	1/31/33	0.96	1.59	1.00	1.00	0.90	....	15
	16	2/ 3/33	Partial pancreatectomy (20 Gm.)						
163	16	2/19/33	2.31	2.87	2.70	2.55	2.55	4.70	14.6
164	16	3/ 6/33	2.04	3.56	3.11	3.00	3.15	5.10	14.1
165	16	4/19/33	3.59	3.70	4.46	3.98	3.06	8.40	13.8
	16	4/20/33	Section of the splanchnic nerve						
166	16	5/ 7/33	2.77	2.88	2.80	2.64	2.70		
167	16	5/22/33	2.58	3.00	3.21	2.97	2.60	6	14
168	16	6/10/33	2.88	2.97	3.49	3.15	3.21	6.10	13.5
169	16	6/25/33	2.15	2.51	2.86	2.48	2.20	4.90	13.1
170	16	7/26/33	1.90	2.21	2.55	2.30	1.89	5.13	13
171	16	8/22/33	2.28	3.00	3.74	2.11	2.18	4.87	12.8
172	16	8/26/33	Extirpation of the transplanted part of the pancreas (7.5 Gm.)						
173	16	8/26/33	4.23						
174	16	8/28/33	5.18	....	....	....	....	16	12.3
175	16	8/30/33	3.87	....	....	....	....	11	12.1
176	17	2/ 1/33	0.95	1.28	0.88	0.95	0.89	....	11
177	17	2/ 8/33	0.97	1.34	0.87	0.81	0.92	....	11
	17	2/13/33	Partial pancreatectomy (12 Gm.)						
178	17	2/28/33	1.95	3.11	3.25	1.85	2.01	4	10.4
179	17	3/16/33	2.21	3.06	3.59	2.00	2.19	2.88	10.5
180	17	4/16/33	2.10	2.52	2.91	2.70	2.00		
	17	4/18/33	Section of the splanchnic nerve						
181	17	5/ 3/33	1.83	2.35	2.85	1.90	1.85		
182	17	5/19/33	1.91	2.77	2.74	2.35	1.90	3.70	10.3
183	17	6/ 5/33	1.60	2.44	2.50	2.28	1.72		
184	17	6/21/33	1.58	1.97	1.99	2.00	1.63	3.65	10.5
185	17	7/22/33	1.49	2.00	1.88	1.94	1.56	3	10.5
186	17	8/25/33	1.77	2.47	2.89	1.89	1.64		
	17	8/27/33	Extirpation of the transplanted part of the pancreas (4.7 Gm.)						
187	17	8/27/33	3.13	3.78	3.65	2.67	2.98	9.70	10
188	17	8/29/33	4.58	....	....	....	....	12	9.7
189	17	8/30/33	4.10	....	....	....	....	8.90	9.5
190	18	2/10/33	1.02	1.45	0.90	0.87	0 90	....	11.9
191	18	2/15/33	1.05	1.47	1.01	0.99	0.89	....	11.8
	18	2/18/33	Partial pancreatectomy (8 Gm.)						
192	18	3/ 8/33	1.33	1.67	1.46	1.29	1.36	0 90	11.4
193	18	3/22/33	1.49	1.68	1.71	1.54	1.50		
194	18	4/ 6/33	1.78	2.05	2.15	2.00	1.69	1.25	11.4
195	18	4/27/33	1.66	2.28	2.54	2.00	1.77	1.30	11.5
	18	4/30/33	Section of the splanchnic nerve						
196	18	5/15/33	1.38	1.70	1.91	1.49	1.41	1	11.1
197	18	5/30/33	1.22	1.24	1.17	1.16	1.20	0.78	
198	18	6/16/33	1.30	1.51	1.57	1.29	1.19		
199	18	6/30/33	1.17	1.23	1.35	1.15	1.15	1.10	10.9
200	18	7/25/33	1.41	1.63	1.71	1.30	1.34		
201	18	8/24/33	1.50	1.74	1.88	1.44	1.36	1.50	11.3
	18	8/28/33	Extirpation of the transplanted part of the pancreas						
202	18	8/28/33	2.45	3.48	3.56	3.09	2.39	5.60	11
203	18	8/30/33	3.70	4.76	5.43	4.23	4.10	9.78	10.7
204	18	9/ 2/33	4.67						
205	18	9/ 2/33	4.00						

on the contrary, the adrenals were much more congested two weeks after intervention (fig. 3), and the vascular congestion was clearly visible also in the cortical tissue. In dogs killed in later periods the

Fig. 1.—Liver two weeks after denervation of the hilus.

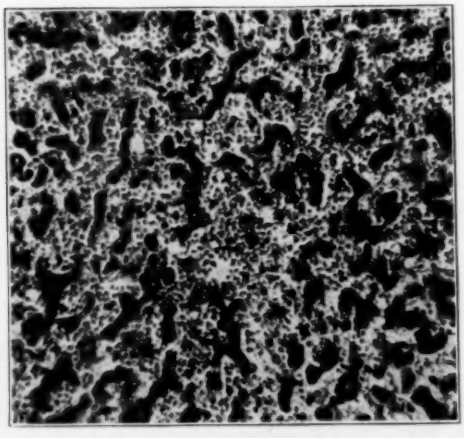

Fig. 2.—Liver two weeks after bilateral section of the splanchnic nerve.

connective tissue was markedly increased, especially in the medullary part, where the cells were small with faintly staining kernels; the chromaffin test with Wiesel's method gave a weakly positive or even a negative reaction. Other organs were normal.

Summarizing the foregoing biochemical and histologic data, I may say that in general I have observed the same results as in animals deprived of the medullary adrenal tissue. In short, the same changes of the fasting blood sugar toward the minimum normal values were observed. Sometimes there were slight, flighty drops below normal, but these were never marked or accompanied by noticeable outward signs. The blood sugar curves in the dextrose tolerance test also were somewhat lower in general than before intervention; in some cases no change took place (experiments 47 and 62). These essential facts observed agree substantially with the statements of other authors. On the basis of such data a better carbohydrate tolerance has been claimed. On these findings were founded the hopes of surgical therapy for diabetes.

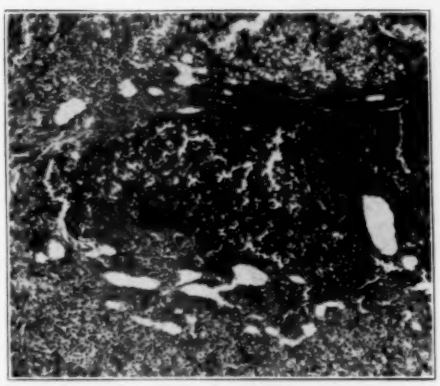

Fig. 3.—Adrenal gland two weeks after bilateral section of the splanchnic nerve.

The similarity of the findings after various interventions (denervation of the liver or suppression of the adrenal function by denervation of the adrenals, medullectomy or splanchnicotomy) proves again the existence of a hepatic-adrenal-sympathetic chain, whose blocking, in any district or in one of the stations along it, has no practical influence, in its final effects, on the sugar content of the blood. On the basis of such phenomena, can a better sugar tolerance be claimed? May a favorable influence on the experimental diabetic condition be alleged? I doubt it very much.

The fasting blood sugar, as has been stated, presents in dogs after denervation of the liver, and more markedly after bilateral splanchnicotomy, variations toward the lower limits of normal values, which, however, cannot lead to any definite conclusions. The figures considered by most authors as representing the normal sugar content of the blood in dogs range from 0.73 to 1.06 per cent; but these authors have not mentioned Negrin's opinion, not shared by all of them, that the sugar

content of the blood in dogs and cats is unstable, or Bang's opinion, which is hardly acceptable, denying even the possibility of defining the average in these animals. I believe that the findings of the dextrose tolerance test, as well as the readings for the fasting blood sugar, can be explained as will be stated.

Since Albertoni's excellent research, it is well known that the liver regulates the distribution and consumption of the dextrose that arrives through the portal circulation, functioning, according to the galenic simile, as a great storehouse in a well governed city. Albertoni in his experimental search for the seat of the changes in carbohydrate in the body, observed that in rabbits after twenty-four hours of fasting relatively large quantities of dextrose (20 Gm.) are withheld by the liver, not interfering, therefore, with the sugar content of the blood. This observation of the Italian physiologist is confirmed by many clinical and experimental observations published in medical literature.

The blood sugar curves in the dextrose tolerance test are probably influenced, moreover, by the condition of the barrier which the liver interposes between the intestines, which are the source, and the general circulation, which is the route of distribution, of the carbohydrates. In fact, Löffler, Grunke and Hess, Pollak, Wachsmuth and Löweneck and previously Hetény (1926) explained the smaller rise in the blood sugar or its failure to change if the introduction of carbohydrates is preceded by injection of ergotamine (more marked if atropine is associated) by the slowing of the portal-hepatic circulation and the consequent smaller deposition of glycogen, which is in turn associated with a correspondingly evident increase of fat. The scarceness of glycogen in the liver and the consequently more active fixation of the dextrose arriving from the portal circulation would explain, according to the conclusions of Albertoni, confirmed by others, the curves with a lower apex and the nearly level curves.

The mechanism of the hyperglycemia that occurs after administration of sugar has been the subject of much debate in past years. Some authors (Zunz and La Barre) have described the involvement of central and peripheral actions due to the dextrose itself, and others (Staub, Traugott, Pollak, Eisnar and Forster, Depisch and Hasenhörl) have mentioned the probability of a reflex action of the mucosa of the duodenum on the liver. On the other hand, the so-called reabsorption theory (Pollak, Gigon, Cori, Staub and La Barre), as well as the theory of stimulus (Rubino and Varela, Umberg, Rosemberg, Hetény and Pogany), is certainly as susceptible to criticism as that which I have adopted. My theory, moreover, is more generally accepted and is supported by experimental and clinical evidence.

I have already mentioned the intense stasis which takes place in the liver after denervation of its stem; this was described also by

de Fermo [38] and closely resembles that which takes place after denervation of the adrenals or removal of the adrenal medullary tissue (Ljvraga [44]). Such hyperemia reaches its maximum after bilateral splanchnicotomy, extending to nearly all the areas which are supplied by these nerves, as has been reported by Pende and Pellegrino. Moreover, I showed the consequent lessening of the glycogen by histologic methods, confirmed by measurements made by Pflüger's method; this phenomenon was produced under the same conditions also by Pico Estrada and by Houssay and his school.

These two positively ascertained facts are in themselves capable of explaining the blood sugar readings after fasting and in the dextrose tolerance test. On this point I must recall my interpretation of the so-called *Karenzhypoglykämie* (Mansfeld's phenomenon) after massive ligature of the pancreas. A fall in the sugar content of the blood was observed twenty-four hours after such intervention and became more marked after two or three days of fasting.[5]

Some authors have reported, besides a better carbohydrate tolerance in general, a lower hyperglycemia after administration of epinephrine and a greater sensibility to insulin. Since epinephrine causes a discharge of glycogen from the liver, mobilizing the dextrose stored there in condensed form, it is evident that the smaller deposit or almost complete lack of glycogen is the cause of the lower hyperglycemia after administration of epinephrine; it is therefore unnecessary to state that the reaction is hindered by an increase of insulin in the blood.

I maintain this opinion also because in nature the simplest explanations are always those which are most probably true (Murri). The foregoing conclusion, moreover, accounts for the higher sensibility to insulin, because the liver's aid in the return to normal of the blood sugar is unstable.

CONCLUSIONS

The ligature of ducts and the massive ligature of the pancreas have proved failures as possible surgical cures for diabetes.

The conclusions of a previous paper of mine [5] have been openly confirmed by de Takáts and his co-workers [45] and Hüttl,[1] who tried the operation on man, and by Linhardt's significant silence.

In the modified pancreas, atrophic tissue, which has lost its external secretive function in the involution caused by inactivity, has been mistaken for functionally active insular tissue, which, indeed, it resembles morphologically. This fact explains why some authors have been led to describe, histopatholgically, insular hyperplasia and regeneration, which however did not correspond to an increase in the secretion of insulin proved by permanent improvement or real clinical recovery. I have

45. Footnotes 2, 29, 30 and 33.

proved instead in the paper to which I have referred that the production of insulin is low after such intervention. This fact is established by the low urinary elimination (demonstrated by Collip's method), by the behavior of the blood sugar when tested by administration of dextrose and by the hepatic glycogen, determinations of which were made in freshly killed dogs by Pflüger's method.

The ligature of the ducts of the salivary glands in general, and especially of the parotid gland, has given results which do not encourage this practice. Two reasons for this failure are the lack of evidence of an increased internal secretion capable of lowering the abnormally high sugar content of the blood, which view I have already set forth (1932),[46] and the inability of the intervention to increase, as some authors believe, the insulin-producing activity of a pancreas having an altered insular tissue and therefore incapable of responding. This procedure, which because of its easy execution could be performed even on ambulatory patients (Gohrbandt), has now lost all credit.

The methods whose purpose is to weaken the anti-insulinic system of organs in order to restore the balance lost by the weakening of the blood sugar reducing mechanisms, especially the pancreas, have not justified the hopeful trust placed in them. Perhaps the choice of the cases in which such intervention is advisable is rather difficult. De Takáts [2] suggested two tests, resistance to insulin and certainty of reaction to ergotamine. Ciceri and Gabrielli [32] suggested previous splanchnic anesthesia as a test.

According to Pollak's investigations, the problem is unfortunately not so simple. He observed that in patients whose blood sugar was favorably influenced by ergotamine the drug would suddenly and without any appreciable reason become apparently inactive. Pollak stated moreover that, although the sugar content of the blood was nearer to normal, he had not been able to observe improvement in the general conditions or an increase in weight after treatment by insulin. This statement is confirmed by an observation of Giordano in 1 of his patients submitted to bilateral denervation of the adrenals. In this case the sugar content of the blood diminished, as did the urinary excretion of sugar, but nevertheless the diabetic gangrene existing was uninfluenced.

In my previous publications it was stated that the predominance of this antagonistic system is not to be considered as absolute, but in relation to the opposing neurohormonic constellation (Pende).

Therefore, referring to intervention on the adrenals, I then expressed my apprehension that, since persons suffering from diabetes maintain

46. Ljvraga, P.: Studio sperimentale sulla legatura dei dotti escretori e sulla enervazione delle ghiandole salivari con speciale riguardo alla glicemia. Riv. di pat. sper. **8**:68, 1932.

their physiologic volume of epinephine, the intervention might provoke an adrenal insufficiency in subjects already suffering from an insular insufficiency. This view was confirmed by a communication from Wilder, Foster and Pemberton,[16] who observed an improvement of the diabetic condition after total thyroidectomy, which, however, was associated with the appearance of the first signs of myxedema; in this condition I have previously described hypertrophy and hyperplasia of Langerhans' islands.[47] Thyroid extracts improved the condition but caused a return of the diabetes.

Rogoff [21] referred (1936) to a case of Addison's disease in a man aged 25, following bilateral denervation, in two stages, of the adrenal glands as an antidiabetic measure. About seven months after the second intervention, the first signs of a subacute hypoadrenalism appeared, which resulted in the patient's death in the course of a year. On the basis of this case Rogoff was drawn to share fully with me the opinion I have expressed: "This case illustrates the serious danger of attempting adrenal surgery for the correction of various ailments supposedly related with disturbed adrenal function."

The denervation of the stem of the liver in turn has proved to deserve no better consideration as a surgical cure for diabetes. The lowering of the sugar content of the blood both during fasting and after administration of dextrose in dogs with mild experimental diabetes from partial pancreatectomy does not suggest, when compared with that in normal dogs, any evident improvement of the diabetic condition. This observation, which applies also to those interventions which attack the adrenals, either in their tissue or in their function, is confirmed by other observations of the negative influence these operations exert on the severe experimental diabetes provoked by pancreatectomy. Komatsu,[39] Depisch, Hasenhörl and Schönbauer [34] and other authors have expressed agreement with this view. In fact, the short successive course of the disease was the same as is usually observed after pancreatectomy, as stated in my previous papers.

The observations of Elias and Waller [48] make still more difficult the far from simple interpretation of the conditions observed after extirpation of portions of the pancreas. These authors observed in dogs a spontaneous improvement of the renal excretion of sugar after a short time, while the carbohydrate tolerance increased and even surpassed the normal level. Successive partial extirpations had the same effect as long as the remaining part was not too small. Similar research by Komatsu [39] gave like results.

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47. Ljvraga, P.: Effetti della tiroidectomia sulle isole di Langerhans, Ztschr. f. Zellforsch. u. mikr. Anat. **22**:232, 1935.

48. Elias, H., and Waller, in discussion on Depisch, Hasenöhrl and Schönbauer.[34b]

It can then be concluded that in procedures affecting the hepatic-adrenal-sympathetic chain, as in those affecting the pituitary or the thyroid gland, some influence is certainly exerted on factors involved in the metabolism of carbohydrate, but only in an unstable manner and after occasional stimulation. They are all, in general, so to speak, accessory safety regulators of the blood sugar; moreover, sometimes the changes in the sugar content of the blood may even be due to secondary interferences, as often happens in natural phenomena with a large field of action.

To mention again the denervation of the stem of the liver, I must finally recall that the effects of this intervention are also partly annulled, at least in the extrainsular forms of diabetes, by the facts brought out by Macleod and Pearce,[35] Pollak, Freund and Schagentweit, Ljvraga and others. These authors proved, in fact, that epinephrine retains its hyperglycemia-producing power even after denervation of the liver; Elliot[49] therefore concluded that epinephrine acts, not on the nerves, but more peripherally, on what he calls the myoneural junction, which Langley has called the receptive substance.

References not cited in this article are to be found in my previous papers (footnotes 5, 6, 44, 46 and 47).

49. Elliott, T. R.: The Control of the Suprarenal Glands by the Splanchnic Nerves, J. Physiol. **44**:374, 1912.

BENIGN TUMORS OF THE BREAST

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Fibroepithelial tumor (fibroadenoma) occurring in the female is of special interest, not only because it is entirely benign but also because, as it occurs frequently in young persons, the physician is often called on for reassurance.

In the six year period from 1931 to 1936 inclusive, 2,585 patients consulted the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital (formerly Stuyvesant Square Hospital) for disorders localized in the breast (table 1).

TABLE 1.—*Diseases of the Breast*

Condition	Cases	Percentage
Definitely benign tumor	722	28.0
Probably benign*	59	2.3
Malignant tumor†	469	18.0
Probably malignant tumor*	41	1.5
Functional disturbance	1,028	40.0
Inflammatory conditions	215	8 2
No pathologic condition	51	2.0

* Clinical diagnosis without pathologic examination.
† Including 449 carcinomas, 18 instances of Paget's disease, 2 sarcomas, 1 melanoma.

The benign tumors included adenoma, cystadenoma, fibroadenoma, fibroma, galactocele, hemangioma, lipoma, lymphangioma, neurofibroma and papilloma.

It is of interest that benign tumors outnumbered malignant tumors. Some years ago statistics showed a reverse order, for at the Halstead Clinic 80 per cent of tumors were malignant, while Erdmann [1] found 56 per cent to be malignant. In the present series only 39 per cent were malignant. This decrease probably indicates a more intelligent attitude of the public, reflected in an earlier consultation of the physician than was customary a few years ago.

The present paper will deal only with benign fibroepithelial tumors which have been removed surgically and of which the diagnosis has been confirmed by pathologic examination.

From the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, Columbia University (Carl Eggers, M.D., Attending Surgeon).

1. Erdmann, J. F.: Tumors of the Breast, South. Surgeon **3**:277 (Dec.) 1934.

The records show that there were 174 cases of surgically treated fibroadenoma of the female breast. There were also 39 cases of fibroadenoma of the male breast so treated, but this series has been presented elsewhere.[2]

CLINICAL PICTURE

Constitutional Type and Age Incidence.—There may be inherited predisposition to mammary tumor, possibly on an endocrine basis. Burkhardt observed fibroadenoma in the left breast of each of twin girls. The tumor was of the same character in each of the two. This would seem to point to the possibility of familial influence.

The patients in my series were well developed and, in the main, well nourished. The slender, boyish type [3] of figure was infrequent. Some of the patients were of a nervous constitution, but in general there were no outward signs which might be said to be characteristic of the presence of a growth.

The age range is shown in table 2.

From these figures it is seen that the earliest age at which the "lump" was first noticed was 11 years and the latest 64. Sellers

TABLE 2.—*Age Incidence of Fibroadenoma*

Age	10-15	15-20	21-25	26-30	31-35	36-40	41-45	46-50	51-55	56-60	61-65
Number of cases	4	44	47	33	18	16	7	2	1	2	1

reported the occurrence of a large fibroadenoma in a girl aged 12; this is exceptional. If the age incidence of fibroadenoma of the female breast is expressed by a graph, it is clear that there is a steep rise, which reaches a peak at the age of 23 and abruptly descends after the thirtieth year. These figures are based on information given by the patients, which is necessarily inaccurate, since a relatively longer period must have elapsed before the tumor attracted notice. Taking into consideration the slow growth of most such tumors, one may assume that the growth probably arises at puberty or shortly after. Coinciding with the onset of menstruation at an average age of 13, such tumor formation would seem to correspond to the active sexual life of the female. If this graph is compared with that obtained from the study of benign fibrous tumors of the male breast it is seen that in the female breast this type of tumor develops most frequently under the age of 30, while in the male a second peak of incidence is found between the fiftieth and the eightieth year. One may say, then, that benign tumors of the breast seem to develop in the male during adolescence and senility, that is,

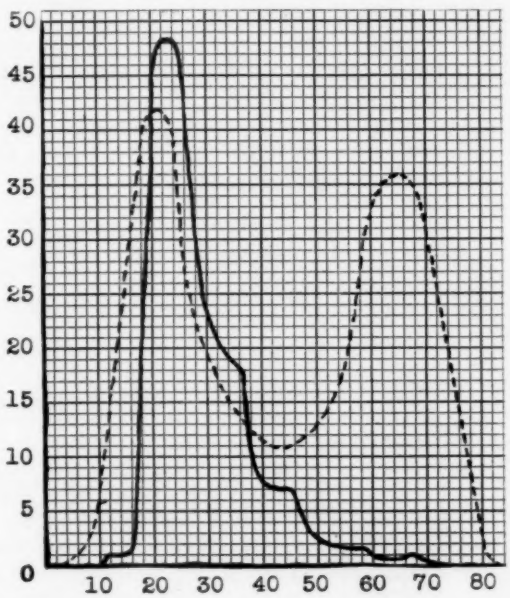
2. de Cholnoky, T.: Benign Fibrous Tumors of the Male Breast, Am. J. Surg. **30**:298 (Nov.) 1935.

3. Taylor, H. C., Jr.: Evidence for Endocrine Factor in the Etiology of Mammary Tumors, Am. J. Cancer **27**:525 (July) 1936.

during periods of life in which endocrine disturbances are most likely to occur, whereas in the female such formation seems to take place at about the second decade of life, that is, when endocrine activity is most intense.

In this series all patients were white except 1, a Negress aged 25 in whom fibroadenoma developed in both breasts within a period of five years.

Marital Status.—In this series 71 patients were single, 91 married, 3 divorced and 3 widowed. The marital status of 6 was unknown.



Incidence of fibroadenoma of the breast. The continuous line shows the distribution of fibroadenoma of the female breast. The interrupted line illustrates the occurrence of fibroadenomas of the male breast, multiplied by 6 (ratio 1:6). The vertical numbers indicate the number of cases; the horizontal numbers, the age incidence.

Occupation.—The patients were classified as to occupation as follows: housewives, 86; office workers, 48; saleswomen, 12; factory workers, 8; telephone operators, 4; and miscellaneous, 16.

Family History.—It is of interest that 23 (13.2 per cent) reported the occurrence of malignant tumors among blood relations, but this percentage is only slightly higher than that commonly accepted for cancer, 10 per cent, and is probably of no significance. A history of "tumor" in the family was given by 4 other patients. These histories may be analyzed as follows: For 7 patients there was a history of

carcinoma of the stomach, the lip, the larynx or the mouth of the father; 9 stated that the mother had died of carcinoma of the stomach or of the nose; 3 described the occurrence of carcinoma in the grandmother, and 1, in an uncle; 3 patients had sisters who had been operated on for "breast tumors."

TABLE 3.—*Number and Percentage of Excised Tumors* *

	Number Among Benign Tumors				Total	
	Female	Percentage	Male	Percentage	Number	Percentage
1. Malformations						
Accessory breast	36	5.2	..	....	36	1.4
Accessory nipple	7	0.8	..	....	7	0.2
2. Fibroepithelial tumors						
Adenoma	40	5.5	..	....	40	1.6
Fibroadenoma	174	29.5	39	5.4	213	8.2
Papilloma						
Nipple	3	0.3	0	....	55	2.1
Skin	23	1.0	3	0.2	26	1.0
Duct	26	1.2	0	....	26	1.0
3. Cystic tumors						
Cystadenoma	220	30.4	..	....	220	8.6
Galactocele	2	0.02	..	....	2	0.07
Sebaceous cysts	60	7.6	11	1.5	71	2.4
4. Connective tissue tumors						
Fibroma	20	2.8	4	0.2	24	1.0
Lipoma	26	3.7	1	4.0	27	1.0
Hemangioma	9	1.0	..	...	9	0.3
Lymphangioma	2	0.2	..	...	2	0.07
Neurofibroma	3	0.3	..	...	3	0.1

* Diagnosis confirmed by pathologic report.

TABLE 4.—*Comparative Incidence of Benign and Malignant Tumors*

All tumors (50% of all cases of mammary disease)		1,291
Benign	781 (61%)	
Malignant	510 (39%)	
Fibroadenoma		
Total patients (20.9% of all tumors and 34.5% of benign tumors)	270	
Operated on	174 (64%)	
Female patients	229 (85%)	
Male patients	41 (15%)	
Male patients operated on	39 (96%)	
The ratio of 270 fibroadenomas to malignant tumors (510) approximates 1:2		

Personal History.—The average age at onset of menstruation was 13 to 14. For only 8 per cent of the patients was the age of onset 16 or 17. In the majority of cases the periods were regular. In 8 per cent they were irregular, and dysmenorrhea was noted in 10 per cent. Pregnancy has been experienced by 48 patients (27.5 per cent), and these had had from one to five children. Five, or 3 per cent, had a history of miscarriage. These facts would seem to bear out Taylor's statement that fibroadenoma is found most frequently in nulliparas (63 per cent) with relatively undeveloped pelvic organs. The develop-

ment of the growths, according to my observations, does not seem to be influenced by marital status or by pregnancy.

The length of time elapsing between observation of the "lump" by the patient and the seeking of medical advice ranged from one week to twelve years. The following table gives the time distribution:

TABLE 5.—*Duration of Lesion Before Examination*

Cases	Time from First Noting of "Lump" to Seeking of Advice
10	1 week
16	Within 1 month
29	Within 3 months
24	Within 6 months
10	Within 1 year
32	Within 2 years
11	Within 3 years
6	4 years
4	5 years
9	6 years
3	10 years
5	12 years
15	Not known

In only 1 case was the growth discovered in the course of routine physical examination. The patient had come to the clinic for advice relating to another ailment.

Personal Surgical History: Abscesses occurring in the same breast in which the tumor was localized were mentioned in the history of 2 of my patients. A previous hysterectomy had been performed on 1 patient at the age of 28. A year previously she had been operated on for fibroadenoma of the breast, of five years' duration. One patient had undergone thyroidectomy. Two had thyroid goiter seven years after the surgical removal of a mammary tumor (?), and 1 had cancer two years after operation. Radical mastectomy was performed on 2 patients, aged 45 and 43 respectively, in whose cases mistaken clinical diagnosis of carcinoma had been made.

Localization.—In 88 patients the tumor was localized in the right breast, and in 86, in the left.

The growth was situated at the upper outer quadrant of the right breast in 44 instances, at the lower outer quadrant in 10, at the upper inner quadrant in 8, and at the lower inner quadrant in 5; it was situated in the upper middle toward the head in 3, to the left of the midportion in 3, to the right of the midportion in 5 and caudad at the midregion in 5; it was located centrally in the breast in 2, and the location was not stated on the chart in 3. It is interesting to note from these figures that 50 per cent of tumors of the right breast occur in the upper outer quadrant. This percentage is raised to 61 if one includes the tumors in the borderline of this section.

The distribution of tumors of the left breast was similar except that there was a slight preponderance of growths localized in the outer quadrants.

The study of age in relation to location showed nothing significant.

Multiplicity and Recurrence.—The tumors were single in the great majority of cases. Geschickter [4] reported an incidence of bilateral involvement of 17 per cent, and Smith and Mark, of 3 per cent. Oliver and Major [5] reported a percentage of 15.75 per cent. In my series 6 patients (3.4 per cent) had tumors in both breasts simultaneously. Four had one tumor in each breast, and 2 had two in the right breast and one in the left; in all, the lesions had developed during a period of five years. In 2 cases the tumors were multiple (1.4 per cent) and appeared in the right breast within a few months.

Recurrence after complete removal of the tumor does not take place, but recurrence in the sense of new tumor formation in the same area, elsewhere in the breast or in the other gland is sometimes observed. An instance of this sort is the case reported by Payer, who removed nine fibroadenomas from both breasts of a young woman within four years. In my series recurrence took place in 6 patients (3.4 per cent); in 5 it was observed within two years, and from 1 five tumors were removed from the same gland within one year.

Size.—The size of the tumor usually varies with the duration, but in this series no definite relation between duration and size could be noted. The growth of the tumor is slow, although some patients exhibit a more rapid growth than others within the same period. Even considering the fact that a tumor may remain unnoticed for a long period, one must admit that some growths are "stationary." Several patients definitely stated that the lump had remained about the same size for years. Others observed rapid increase in its size within weeks or months.

Six patients were examined early, when the round or oval tumor was about 5 mm. in diameter. Eighteen when first seen had a lump 1 cm. in diameter. In 28 cases the size of the tumor was 1.5 cm.; in 36, 2 cm.; in 18, 2.5 cm.; in 10, 3 cm.; in 15, 4 cm.; in 9, 5 cm.; in 4, 6 cm.; in 4, 7 cm. Six patients had tumors 8, 9, 10, 12 and 15 cm. in diameter. In 20 cases no exact measurements were noted. The largest tumor measured 15 by 12 cm. It was removed from the breast

4. Geschickter, C. F.; Lewis, D., and Hartman, C. G.: Tumors of Breast Related to the Oestrin Hormone, Am. J. Cancer **21**:828 (Aug.) 1934.

5. Oliver, R. L., and Major, R. C.: Cyclomastopathy: Physiopathological Conception of Some Benign Breast Tumors, with Analysis of Four Hundred Cases, Am. J. Cancer **21**:1 (May) 1934.

of a patient aged 38, who had had the growth for five years. Approximately three fourths of my patients came for operation before the tumor had reached a diameter of 3 cm.

Fibroadenomas of enormous size have been reported. In Ashwell's case the tumor had a gross weight of 29 pounds (13.2 Kg.). Mackenzie [6] described one weighing 35 pounds (15.9 Kg.); the patient had been for years in the hands of religious revivalists and faith healers. Vos [7] made a comparative study of the fibroadenomas occurring in the white and in the native population of the colonies of the Netherlands and found that in the natives the growths attained a decidedly larger size before a surgeon was consulted.

ETIOLOGY

Trauma was mentioned in 3 per cent of my own cases, but the patients were unable to state the exact location of the injury, which was commonly designated as a "baby kick" or some similar mild trauma. One patient, 44 years of age, in whom the tumor was of four months' duration, attributed it to a kick by a horse suffered seven years before! It seems to me that trauma plays a minor role, if any, in the causation of the tumor, and that it serves rather the function of revealing a tumor already present.

While the causes underlying the formation of fibroadenoma are still being sought, clinical and some experimental evidence indicates that it is probably due to some hormonal influence. Since the presentation of Ribbert's theory of embryonal rests which have lost their correlation with the remainder of the mammary gland, Dietrich, Fragenheim, Moszkowski and others have concluded that chronic mammary disease is responsible for the development of fibroepithelial tumor.

Stimulus for further research was imparted by Rosenburg's [8] observation that the breast takes part in the sexual cycle and that it is influenced by the corpus luteum, of which the effect is most pronounced in the premenstrual period. He also found that there is a certain neoformation of tubules and acini before menstruation, which disappears with cessation of the periods.

There is a stimulus to growth at puberty and during the following years until the mammary glands mature. This may be so great that tumors result in the developing tissue, especially at the onset of men-

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6. Mackenzie, K.: Huge Fibro-Adenoma of the Breast, Brit. J. Surg. **23**:234 (July) 1935.

7. Vos, J. J. T.: Effect of Pregnancy on Benign Tumors, Geneesk. tijdschr. v. Nederl.-Indië **73**:1497 (Nov. 21) 1933.

8. Rosenburg, A.: Ueber menstruelle, durch das Corpus luteum bedingte Mammaveränderungen, Frankfurt. Ztschr. f. Path. **27**:466, 1922.

struation (Dawson).[9] That there is a genuine hormonal effect has been shown by Watson and others, who observed that marked development of the breast may be induced by administering estrogenic substances to hypogonadal, amenorrheic girls.

It is assumed that the main factor in tumor formation is the so-called estrogenic hormone. Fibroadenoma may also arise in consequence of some ovarian dysfunction which may not be so pronounced as to produce irregularity of menstruation or disturbance in fertility. This theory is supported by the fact that fibroadenoma develops only exceptionally before puberty and rarely after the menopause. It seems, therefore, that ovarian function is essential to the development of such a tumor, although it is not necessarily the specific cause (Taylor).[3]

Diffuse virginal hypertrophy of one breast is not uncommonly accompanied by the occurrence of fibroadenoma (Geschickter) which is dependent on the duct epithelium and on the surrounding mammary tissue.

It may be said that cyclic proliferation induced by hormonal influence on certain areas is followed by incomplete regression at each cycle, which may result in tumor formation receiving fresh stimulation from each new cycle; that is, if epithelial hyperplasia takes place with faulty regression and the affected lobules undergo further proliferation at a succeeding cycle, this may result in the formation of an adenoma. If the chief fault is an overgrowth of fibrous elements exerting pressure or pull on the proliferating epithelium in the premenstruum, this may result in fibroadenoma of the ordinary intracanalicular type (Ingleby).[10]

It is possible, however, that other glands besides the ovary may influence the formation of fibroadenoma; for example, the anterior lobe of the pituitary, although this seems problematic. Gonadotropic substance from the urine of pregnant women (antuitrin S), an extract of the anterior lobe of the pituitary gland (antuitrin G) and an estrogenic substance (theelin) in combination produced a definite increase in mammary hyperplasia in rats, leading to benign fibroadenoma (Heiman and Krehbiel).[11] It is known that the ovary activated by the pituitary gland exerts a certain influence on mammary tissue. Furthermore, the anterior lobe of the pituitary and the mammary glands are certainly related (Culpepper).[12]

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9. Dawson, E. K.: A Histological Study of the Normal Mamma in Relation to Tumour Growth, Edinburgh M. J. **41**:653 (Dec.) 1934.

10. Ingleby, H.: Relation of Fibro-Adenoma and Chronic Mastitis to Sexual Cycle Changes in the Breast, Arch. Path. **14**:21 (July) 1932.

11. Heiman, J., and Krehbiel, O. F.: The Influence of Hormones on Breast Hyperplasia and Tumor Growths in White Rats, Am. J. Cancer **27**:450 (July) 1936.

12. Culpepper, A. L.: Breast Tumors as Related to the Anterior Pituitary Gland, New Orleans M. & S. J. **87**:39 (July) 1934.

Lewis and Geschickter [13] found increased estrogen in patients with fibroadenoma. This was confirmed by Kahler [14] and established the power of fibroadenoma to concentrate estrogen. Recent experiments by Mohs [15] on white rats failed to show that the estrogen concentration in transplantable fibroadenoma is greater than that in surrounding tissues. Fibroadenomatous transplants develop in males and also in spayed females, though less often and less rapidly. In such cases the amount of estrogen in the body is very small; therefore, it is unlikely that estrogen is the factor stimulating to growth, and the fibroadenoma would seem to be a true neoplasm. It responds to estrogen because it derives from breast tissue. Mohs concluded that fibroadenoma in the experimental animal does not owe its growing ability to concentration of estrogen within itself.

Disturbance of the balance of hormones within the sexual cycles may be considered the most important factor in causation of fibroadenoma, but the mechanism of production still remains obscure. In a former article I expressed the view that fibroadenoma of the male breast has its inception in some hormonal disturbance at the time of puberty and senility.[2] It is interesting to note that in Menville's [16] view fibroadenoma of the male breast would be a further development of gynecomasty. I was unable to confirm this theory, as in my cases of benign fibroepithelial tumor of the male breast, I was dealing with rather localized nonencapsulated tumors without diffuse enlargement of the remaining glandular element.

Considering the different clinical and pathologic picture of fibroadenoma occurring in the male, the theory may be advanced that here the cause might possibly lie in different hormonal stimuli. Enlargement of the male breast has been observed not only in patients with atrophic testicles but also in cases of pituitary tumor (Moehlig).[17] Recently in 1 of my cases a fibroadenoma occurring in a boy aged 15 was accompanied by absence of one testicle. Further studies of the hormonal government of the breast may shed more light on the mechanism by which such a tumor is produced.

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13. Lewis, D., and Geschickter, C. F.: Estrin in High Concentration Yielded by Fibroadenoma of the Breast, J. A. M. A. **103**:1212 (Oct. 20) 1934.

14. Kahler, M. V.: The Bioassay of a Fibro-Adenoma of the Breast for Estrogenic Substance, J. Indiana M. A. **29**:374 (Aug.) 1936.

15. Mohs, F. E.: Lack of Estrin Concentration in Adenofibroma of the Mammary Gland in Rats, Am. J. Cancer **29**:356 (Feb.) 1937.

16. Menville, J. G.: Gynecomastia, Arch. Surg. **26**:1054 (June) 1933; Fatty Tissue Tumors of the Breast, Am. J. Cancer **24**:797 (Aug.) 1935.

17. Moehlig, R. C.: Pituitary Tumor Associated with Gynecomastia, Endocrinology **13**:229 (Nov.-Dec.) 1929.

From the theoretic point of view, tumor formation under hormonal influence may occur as follows:

1.—Increased sensitivity of mammary tissue to normal or nearly normal hormonal products, which may lead in some areas to more pronounced proliferation than in the rest of the tissue, regression then becoming impossible.

2.—Under the increased stimulus of hormonal dysfunction there may be glandular areas which acquire independent growth in the presence of disturbed function.

3.—Hyperconcentration of some hormonal substance may be present, which acts as an irritant, urging to growth, either on the defensive principle (connective tissue) or by excessive proliferation of the entire glandular substance.

The morphologic character of a tumor may depend on the stimulus and on the reaction of the organism. Such a reaction may take the form of control of localized growths or control may gradually break down, leading to malignant neoplasia.

As a working hypothesis it may be conceived that in the organism there are formed "mother compounds" or substances which are used by the various glandular tissues to produce hormones. If the function of the testicles or ovaries is normal, these glands will produce the amount of hormone required to maintain the function of the organism at the individual normal level. Should the sex glands be in a pathologic condition and unable to utilize the "mother compounds" to produce hormones, these compounds may possibly influence the closely related glandular structures, for example, the breast. Such dysfunction may cause excessive proliferation of the epithelial and fibrous tissues, and tumor, either benign or malignant, may result. The theory may also be suggested that the body may be refractory to the available hormones, either because it is immature (pubertal) or because it is senescent. Consequently, the breast may respond to the unused hormones, especially in the male. In the female there may be dysfunction of the ovaries not manifested clinically but producing substances which, although not estrogenic, have power to stimulate the breast tissue to tumor formation. Cystic tumors theoretically may originate in an imbalance of secretory hormones (prolactin, lutein), in addition to the estrogenic substances (Goldzieher).[18]

PHYSIOLOGY

It is of interest that fibroadenoma of the female breast responds to the menstrual cycle. Ingleby [10] was able to demonstrate in the tumor the same type of cyclic changes as in the adjacent normal mammary

18. Goldzieher, M.: Personal communication to the author.

tissues and was able to determine the stage of that cycle from examination of sections of tumor, provided the menstrual cycles were regular.

It has also been found that during pregnancy there is hypertrophy of the epithelium and that during lactation the tumor is modified in a manner similar to the process going forward in the normal breast tissue (lactating adenoma: Hunter,[19] Kilgore; Kreibig;[20] Moran[21]).

Experimentally, transplanted adenoma has been shown to be influenced by the state of lactation, activity concurring at succeeding periods and involution running a parallel course. An adenoma implanted into the peritoneal cavity also shows active secretion, which one can regard as demonstrating a hormonal reaction.

Symptoms.—The chief complaint is that of a "lump." Pain is complained of in about one third of the cases and varies in character and degree. Sharp pain is only rarely noted (2 per cent); moderate pain occurs in 30 per cent of cases; periodical or (rarely) continuous pain, in 2 per cent. The pain is a dull local ache, stinging, pricking or burning, sometimes exaggerated immediately before, during or shortly after menstruation (4 per cent). The pain often radiates to the shoulder or arm, accompanied by sharp local pain. Exacerbation of pain may accompany rapid increase in size of the tumor (Cheatle and Cutler[22]).

Although commonly the breasts are found to be well formed and well developed, they may be small, and one not infrequently observes fibroadenoma in the relatively small, pendulous breast. They may perhaps contain less glandular substance than the normal breast. A few are definitely underdeveloped, while some are of the virginal type of hypertrophied breast. The contour is always smooth though one breast may be larger than the other and may be deformed by a bulky tumor. It may be said that deformity caused by the new growth depends on the size of the tumor and the size of the breast, although a tumor of considerable size may be invisible in a well developed larger gland. A tumor 3 to 5 cm. in diameter may perceptibly increase the size of the breast, provided both breasts were originally of equal size.

The nipple is not retracted by the tumor but is free, although it may be thrust forward or to one side by a bulky growth. I observed no discharge from the nipple in any case in my series, but Geschickter noted this in 4 per cent of his.

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19. Hunter, J. B.: Lactating Adenoma of the Breast, Proc. Roy. Soc. Med. **23**:944 (May) 1930.

20. Kreibig, W.: Ueber das Schwangerschaftsadenom der weiblichen Brustdrüse, Wien. klin. Wchnschr. **43**:972 (July 31) 1930.

21. Moran, C. S.: Fibro-Adenoma of Breast During Pregnancy and Lactation, Arch. Surg. **31**:688 (Nov.) 1935.

22. Cheatle, G. L., and Cutler, M.: Tumours of the Breast: Their Pathology, Symptoms, Diagnosis and Treatment, Philadelphia, J. B. Lippincott Company, 1931.

The skin of the gland is smooth. There is no dimpling or "pigskin" appearance, and no discoloration is perceptible unless trauma has occurred or infection is present. A large tumor may ulcerate (adenofibroma phyllodes) as a result of direct pressure, which causes local trophic disturbance.

On palpation the examiner's hand feels a firm, occasionally soft (1.1 per cent in older patients), solid or elastic (0.8 per cent), well limited, freely movable, smooth or lobulated (4 per cent) tumor.

The hardness or softness of the tumor depends on the relative amount of fibrous tissue or glandular elements present. The new growth is frequently peripheral, beneath the skin or embedded in the mammary tissue and not adherent to the skin. In my series dimpling of the skin and retraction of the nipple were observed in 3 cases (1.7 per cent), the patients' ages being 43, 43 and 19, and in these 3 cases a subsequent clinical diagnosis of malignant tumor was made. The percentage of preoperative error may, however, be higher. Buchanan [23] estimated it at 10.

The fibroadenoma may be round or oval, sometimes elongated. In size it ranges from that of a pea to that of a goose egg; it is rarely larger. In suitable cases transillumination reveals a definite shadow in 50 per cent of cases and a faint shadow in 13.8 per cent. The growth transmits light in 13.8 per cent, is indefinite in 11.2 per cent and is "negative" in 11.2 per cent. (These figures are based on my own findings.) Palpable axillary nodes were present on the same side as the tumor in 15 per cent of cases (hard nodes, 2 per cent). Soft small nodes were found in both axillas in 10 per cent. The following case illustrates the simultaneous development of fibroadenoma and carcinoma.

CASE 1.—Mrs. S. W., a white woman aged 42, a clerk, stated that for six months she had had two lumps in her right breast. Each lump when first noticed was the size of a pea, and each was gradually increasing. Both were sensitive to touch. She had had one child at 18 and had nursed it. The patient's father had died of cancer.

Clinical examination revealed markedly increased consistence of the breast. In the lower inner quadrant of the right breast was a distinctly movable mass about 2 cm. in diameter, and a similar but smaller firm tumor was observed at the lower outer quadrant of the same breast. The axillary glands were not palpable. At the request of the patient the tumor in the lower inner quadrant was removed on Nov. 27, 1931. Pathologically, the well encapsulated growth was reported as fibroadenoma. At the patient's request, the other tumor was not touched. She did not return for the regular follow-up appointments. Two years later she came in with a stony hard, somewhat nodular mass which extended from the lower outer quadrant up the entire upper outer quadrant and which cast a definite irregular shadow. There was some fixation of the nipple and adherence

23. Buchanan, E. P.: Benign Lesions of the Breast, Pennsylvania M. J. **40**: 521 (April) 1937.

of the skin. Numerous firm nodes were palpated in the right axilla. The left breast was entirely normal and transilluminated well. Roentgenograms of the chest and bones revealed no pathologic process. Radical operation for carcinoma of the right breast was performed on Nov. 28, 1933. The pathologic report was carcinoma (grade 2) of the breast and axillary lymph nodes. Healing was undisturbed, and good function of the arm was obtained. Roentgen therapy was given postoperatively. At the present time (1938) the patient is being seen in the follow-up clinic and shows no evidence of local or distant metastases.

This case emphasizes the care necessary in any consideration of so-called "harmless fibroadenoma" or cyst of the breast, and the advisability of removing any tumor so diagnosed. In fact, any lump or lumps in the breast should always be removed, and it should be the rule that frozen sections be made if the condition is at all questionable, for only pathologic examination can definitely rule out malignancy. The fact that one growth proves on removal to be fibroadenoma does not prove the like nature of any other tumor which may be present at the same time. In this case the other proved to be early carcinoma. Furthermore, in the case of malignant tumor in an early stage a timely radical operation increases the chances of permanent cure.

Pathologic Picture.—Essentially, fibroadenoma is a benign tumor presenting the structure of the mammary gland, being composed of connective tissue and glandular elements. Ewing [24] differentiated two gross forms of fibroepithelial tumor of the breast, the massive fibroadenoma and the papillary, or intracystic, fibroadenoma.

The massive fibroadenoma may be diffuse, presenting hypertrophy of neoplastic character, but most frequently the tumor is a well defined, firm fibrous mass. It may, however, be soft and vascular.

On gross inspection the growth is a round, oval or lobulated well encapsulated tumor (except fibroadenoma occurring in the male, which is diffuse) varying from microscopic size to enormous proportions. The color is usually whitish gray. The consistency depends on the structure; that is, if the tumor consists mostly of connective tissue it will be harder than if the epithelial constituents predominate or if there is underlying myxomatous or cystic degeneration. On section, whorl formation is usually seen.

Excessive development of connective tissue about the acini or ducts makes the tumor firm and more fibrous; such a tumor is called pericanalicular or intercanalicular fibroadenoma and occurs in 4 per cent of cases. When the acinic lumen is invaded by the diffuse or papillary fibrous growth the tumor is called an intracanalicular fibroadenoma (86 per cent). The two types are frequently found together in the same tumor (10 per cent of my cases).

24. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

The growth may be a villous or cauliflower-like mass covered by a fibrous capsule with an epithelial lining, which is the dilated acinus. The lining of the glandular portion is normally cuboidal epithelium. Ciliated epithelium was found in only 1 case.[25] In my series chronic cystic mastitis was an associated condition in 3 per cent of all cases and in 11 per cent of patients between the ages of 32 and 50.

It is customary to classify the tumors according to the constituent which predominates. In about 2 per cent of cases the adenomatous element exceeds the fibrous element. The tumor is therefore called adenoma. If more fibrous tissue is present with the predominating epithelial element, a tumor is formed which the pathologist calls fibroadenoma; this may be an adenofibroma if the glandular element predominates or a fibroadenoma if the fibrous tissue is in excess. It would seem sufficient, however, to use the term fibroadenoma in all instances, setting off the varieties with a qualifying adjective, such as "cellular" or "fibrous," according to which constituent is in excess. A tumor in which the acini become obliterated and compressed by the proliferating fibrous tissue to such an extent that the growth appears to be made up entirely of the latter may be confused with the rarely occurring pure fibroma, which is observed in only about 2 per cent of cases. Such a tumor may arise from the connective tissue of the skin, Cooper's suspensory ligaments or the interglandular septums of the breast. According to Beneke, fibroadenoma develops primarily from mature glandular tissue which is essentially epithelial, fibrous tissue being formed only secondarily.

Fibroadenoma may undergo benign or malignant degeneration. Benign degeneration may be cystic (which is of common occurrence) myxomatous or xanthomatous (Haagensen). Cartilaginous elements were observed in 2 cases by Cheatle and Cutler. Of far more importance is malignant degeneration, which may be carcinomatous or sarcomatous. Carcinomatous degeneration is difficult to determine and is a point much disputed. According to Junge,[26] who studied cancer of the breast, examination of the whole gland reveals simple or multiple fibroadenoma in 24 per cent of cases (25 per cent according to Cutler), which may lead to the supposition that this is a concomitant condition in a gland in which disease is generalized. One may assume that carcinoma may develop in a fibroadenoma, but it has been observed only rarely (de Quervain; Geschickter) and that it may be considered a secondary invasion (Cheatle and Cutler; Speese).

25. Buday, K.: Proliferirendes Adenocystom der Mamma mit Flimmerepithelien, Virchows Arch. f. path. Anat. **156**:395, 1899.

26. Junge, W.: Ueber die Beziehungen zwischen der Fibrosis cystica, den gutartigen Tumoren und dem Karzinom der Brustdrüse, Beitr. z. path. Anat. u. z. allg. Path. **88**:595, 1932.

Sarcomatous degeneration, which has been definitely observed (Lörinc; Brites [22]) would seem to be of more importance. Fox [26a] stated that of his 60 collected cases of mammary sarcoma, 41 of the tumors were fibrosarcomas. Of these, 40 per cent were secondary to fibroadenoma or to intracanalicular myxoma, and the entire 57 per cent were found within the substance of a pre-existing fibroadenoma. Cheatle and Cutler stated that sarcomatous degeneration is rare. A number of quickly growing cellular tumors simulate sarcoma, but these do not metastasize.

Experimentally, Heiman and Krehbiel,[11] Oberling,[27] Guérin [28] and others observed sarcomatous degeneration of successively transplanted fibroadenoma in white rats. These were also noted by Picco after a few months of injections of an estrogenic substance.

In no case in my series of benign tumors did sarcomatous changes occur. I agree with Oliver and Major [5] that sarcomatous degeneration, though it may occur, is greatly overemphasized. The incidence of sarcoma among mammary tumors varies from 0.5 per cent (Erdmann) to 2 to 4 per cent, according to different authors. Smith and Mark found such changes in 7 per cent of 201 cases of benign tumor. The percentage in my series was 0.2.

DIFFERENTIAL DIAGNOSIS

As a rule, differential diagnosis is easy, though absolute certainty may be difficult to arrive at in certain cases, as, for example, when the freely movable, well circumscribed, firm, nonadherent growth reveals itself as a well circumscribed carcinoma. This type will be discussed in detail.

Echinococcus or cysticercus cyst of the breast is rare. Reports of single cases of actinomycosis and sporotrichosis of the mammary gland may be found in the literature (von Angerer; [29] Poteau; Quénu).

Diagnosis of maldevelopment, such as aberrant mammary tissue, gynecomasty or accessory nipple, can be readily made and need not be discussed.

Acute Inflammatory Processes.—Acute mastitis may occur in the adolescent, the newborn or the puerperant and is characterized by

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26a. Fox, S. L.: Sarcoma of Breast, with Report of 60 Cases, Am. Surg. **100:** 401 (Sept.) 1934.

27. Oberling, C.; Guérin, M., and Guérin, P.: Recherches sur des greffes en série de tumeurs mammaires benignes chez le rat, Bull. Assoc. franç. p. l'étude du cancer **22:**606 (Nov.) 1933.

28. Guérin, P.: Sarcome à cellules géantes du sein par transformation d'un fibro-adénome latent, Bull. Assoc. franç. p. l'étude du cancer **25:**326 (Feb.) 1936.

29. Angerer, H.: Geschwulstbildungen der Brustdrüse beim Manne, Deutsche Ztschr. f. Chir. **241:**104, 1933.

symptoms of inflammation. In the case of abscess the gland, which in the early stages is firm, has a tendency to resolve, or the inflammation may extend to the surface of the skin. Fluctuation is usually present.

Chronic Inflammatory Processes.—I have observed 5 cases of tuberculosis of the mammary gland. This condition may occur as simple nodules or as cold abscess with fistula. In my series there was 1 case of gumma of the breast, the diagnosis being proved by the Wassermann reaction and by subsequent antisyphilitic treatment.

Functional Disease of the Breast.—There should be no difficulty in making the diagnosis of chronic mastitis, the nodular shotty condition being diffuse and often bilateral. Neither should there be difficulty in recognizing chronic cystic mastitis (Reclus-Schimmelbusch disease), multiple cysts of the breast.

Obviously, benign tumor in the breast may arise from any of its constituent tissues. Among my cases were the following:

Lipoma.—There were 27 cases of lipoma (in 1 of which the tumor occurred in a male), comprising 3.7 per cent of all cases of benign tumor of the mammary gland and 1 per cent of all cases of pathologic conditions of the breast. Kleinschmidt's [30] figure is 2 per cent. Typically, lipoma is a lobulated fatty tumor arising in the subcutaneous fatty tissue. The intramammary and retromammary variety is frequent, and the differential diagnosis between such a tumor and a malignant tumor may be more difficult. Schneyder has described a lipoma of the female breast with total absence of the glandular element. Holland [31] found a lipoma weighing 750 Gm. in the left breast of a male patient.

Hemangioma.—The 9 cases in my series comprised 1 per cent of all cases of benign tumor of the breast and 0.3 per cent of all cases of disease of the mammary gland. Hemangioma may be a well encapsulated, elastic tumor easily excisable, although in some cases it may require extensive amputation of the breast. The simplest form is telangiectasia, but the cavernous form of tumor is most frequently observed. De Pol [32] reported a case of fibroangioma of the male breast.

Lymphangioma.—This growth is of rare occurrence. I observed 2 cases, 0.2 per cent of my cases of benign tumor of the breast and 0.07 per cent of all cases of disease of the breast. It is practically impossible to make a clinical diagnosis. Rarely lymphangioendothelioma and hemangioendothelioma may be observed.

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30. Kleinschmidt, O.: Die gutartigen Mammageschwülste, Chirurg **3**:297 (April 1) 1931.

31. Holland, T. E.: Lipoma of the Male Breast, Canad. M. A. J. **32**:74 (Jan.) 1935.

32. de Pol, G.: Fibro-angioma della mammella maschile, Policlinico (sez. chir.) **41**:679 (Dec.) 1934.

Myoma.—Those which have been observed have in every instance been leiomyoma and located in the region of the areola, originating from the smooth muscle fibers of the corium and adherent to the skin (Kleinschmidt), although cases have been reported in which the tumor was located in the breast proper (Melnick).[33]

Neurofibroma.—In my series there were 3 cases of neurofibroma (0.4 per cent of cases of benign tumor and 0.01 per cent of all cases of mammary disease).

Other tumors of extreme rarity are chondroma, teratoma (of which Coues[34] reported a case, the tumor being the size of a baseball) and xanthoma, which may be observed as a primary growth. It should be noted that fibroadenoma when it occurs in a patient with diabetes may occasionally present xanthomatous degeneration (Haagensen).[35] Neuroma of the nipple has been described by Stewart.[36]

Adenoma.—In my series there were 40 cases of adenoma, 5.5 per cent of cases of benign tumor and 1.6 per cent of all cases of mammary disease. This tumor is well defined and freely movable, moderately firm and rather elastic. Microscopic examination alone will make diagnosis certain.

Cystadenoma.—I observed 200 cases in my series, 30.4 per cent of all cases of benign tumor and 8.6 per cent of all cases of disease of the breast.[37] Cysts may be differentiated by transillumination. If the field is clear they transilluminate well. Fluctuation, if present, is only in the superficial lesion. It is usually absent, owing to tension of the fluid contents.

Fibroma.—This is a well circumscribed, hard, small tumor in the skin or gland. I observed 24 cases, 3 per cent of cases of benign tumor and 1 per cent of all cases of disease of the breast.

Papilloma.—Of this type of tumor I observed 55 instances. Three of the tumors were localized in the nipple, 23 in the skin and 26 in the duct. Three of the patients were male. Cases of papilloma comprised 7 per cent of cases of benign tumor and 2.1 per cent of all cases of disease of the breast.

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33. Melnick, P. J.: Fibromyoma of the Breast, Arch. Path. **14**:794 (Dec.) 1932.

34. Coues, W. P.: A Case of Teratoma of the Breast, New England J. Med. **204**:656 (March 26) 1931.

35. Haagensen, C. D.: Xanthoma of the Breast, Am. J. Cancer **16**:1077 (Sept.) 1932.

36. Stewart, F. W.: Neuroma of the Nipple, S. Clin. North America **13**:434 (April) 1933.

37. Owing to a large number of cases, it is my intention to discuss this condition in greater detail in another paper.

Malignant Growths.—Malignant disease of the mammary gland may take the form of carcinoma, sarcoma or Paget's disease of the nipple.

1. Carcinoma: Differential diagnosis may be difficult in the case of a beginning duct carcinoma, especially if the patient is young. In a patient over 35 a solid tumor is probably a duct carcinoma, since fibroadenoma is comparatively rare at this age (Cheatle and Cutler). When the diagnosis is doubtful, careful and wide excision through the apparently healthy adjacent tissue is indicated to prevent dissemination of a possible carcinoma, and examination of frozen sections is imperative to establish the diagnosis at once. If the growth is malignant, radical mastectomy is done immediately.

When the classic picture of carcinoma is absent, the diagnosis, even when made by experienced observers, carries a factor of error of 3 per cent. Cases in which the growth simulates fibroadenoma comprise about 2 per cent. Yet in cases of this type a correct diagnosis at this early stage is of the greatest importance, since early radical mastectomy increases the chances for permanent cure. Palpable axillary lymph nodes, especially if hard, suggest carcinoma.

The following cases are illustrative:

Case 2.—Mrs. C. R., a white woman aged 43, came to the tumor clinic of the Skin and Cancer Unit on June 3, 1933, for treatment of a small lump in her right breast, which she had noticed the week before. She stated that pain had led to its discovery. She had nursed each of her two children for about nine months, the last one ten years previously. The menstrual history was normal and the medical history noncontributory. The patient's father had died of carcinoma of the throat. The patient was a well developed and well nourished woman with pendulous, apparently normal breasts presenting no change in contour of the nipple. In the upper outer quadrant at the periphery of the right breast, about 6 cm. distant from the nipple, was a firm, freely movable nontender nodule measuring 1 cm. in diameter. The axillary glands were not palpable. A diagnosis of fibroadenoma was made, and excision was undertaken. At operation the tumor was found to be slightly adherent to the surrounding tissues. It was gritty and diffuse, and carcinoma was suspected by the operator. Frozen sections confirmed this suspicion, and radical mastectomy was immediately performed. The pathologist reported scirrhous carcinoma, grade 2, with hyperplasia of the axillary lymph glands. The patient was seen in the follow-up clinic four years later. She was in good condition and free of recurrence.

Case 3.—Mrs. H. H., a white woman aged 38, applied for treatment on Oct. 28, 1931, stating that eighteen months previously she had discovered a small lump in her right breast. Her family physician, whom she had consulted six months previously, did not advise its removal, saying it was benign. The patient had one child, then 14 months old. There was no history of miscarriage. Her sister had a tumor of the breast, of unknown nature. The patient was a well developed and well nourished woman with normal breasts of medium size, showing no change in shape or contour. The nipples were prominent and freely movable. In the upper outer quadrant of the left breast, about 5 cm. from the nipple, was an

irregular, nodular firm mass about 1 cm. in diameter. It was not attached to the skin. There were no enlarged lymph nodes in the corresponding axilla. A diagnosis of fibroadenoma was made, and removal of the growth was advised. The patient postponed the operation and did not return to the clinic for eighteen months. On her return after this lapse of time the tumor was found to have increased to a diameter of 4.5 cm. It was attached to the skin with puckering of the surrounding skin and cast a definite shadow by transillumination. There were five firm lymph nodes in the left axilla. The case presented the classic picture of carcinoma of the breast with metastasis to the regional lymph nodes. Radical operation was performed in March 1933. Pathologic examination revealed medullary carcinoma, grade 2, with axillary metastasis. Two years later, in spite of roentgen therapy instituted after operation, generalized metastases with jaundice and other symptoms developed, and the patient died forty-six months after the operation.

When this type of case is considered it is clear that tumor of the breast occurring in patients past the age of 35 should be considered carcinoma until proved otherwise by frozen section and should be treated accordingly.

2. Sarcoma: In its early stages sarcoma may stimulate benign fibroepithelial tumor, but its unusually quick progressive growth soon arouses suspicion. There were 2 such cases in my series.

TREATMENT

Until better knowledge of the physiologic and pathologic character of the lesion is at hand and until prevention of such growth may be accomplished with the aid of endocrinology, surgical removal remains the only form of treatment. All solid tumors of the mammary gland should be removed, regardless of the patient's age or sex. Such removal is imperative not only to relieve the patient's mind but also because only such removal, supported by pathologic examination, can rule out malignancy. In the second and third decades of life malignant lesions of the breast are rare but they occur, and this fact makes removal the wise course.

The technic employed is a matter of choice, ranging from a simple radial incision, preferably with the patient under general anesthesia, to an esthetic circular incision in the fold of the breast or encircling the areola. Only exceptionally should the growth be enucleated; this may be done, however, for a small, superficial tumor. As a general thing it is recommended that the growth be excised together with the corresponding sector of the breast, in order properly to eradicate the lesion and prevent recurrence. Mastectomy may be necessary in the case of a large, bulky tumor.

Postoperative Results.—Wix [38] reported that after removal of the fibroadenoma 66 per cent of patients had no further complaint, but 34

38. Wix, W.: Das Schicksal der gutartigen, nicht entzündlichen Mammaerkrankungen, speziell der chronischen Mastopathie und des Fibroadenoms, Thesis, Kiel, 1932.

per cent did complain, and of these 21 per cent had pain in the breast which had not been operated on. The pain coincided with menstruation but probably had no relation to it.

Recurrence took place in 3.5 per cent of my cases. Wix reported recurrence in 8 per cent, Lamb in 2 per cent and Geschickter in 10 per cent.

SUMMARY AND CONCLUSIONS

A statistical study is presented of 722 cases of benign tumor of the breast, with a particular discussion of 270 fibroadenomas of the female breast.

Fibroadenoma is a benign tumor which develops shortly after puberty. Such a tumor may arise as a result of disturbance of the endocrine secretory function or of related functions.

Fibroadenoma of the breast in the female, contrary to that occurring in the male, is well encapsulated, freely movable, firm, solid and rarely attached to the skin and surrounding tissues. Exceptionally, it may suggest a malignant growth.

Malignant degeneration did not take place in any of my cases, and its occurrence is doubtful.

Differentially, the greatest risk of error lies in the possible presence of certain types of carcinoma which may simulate fibroadenoma. Certainty can be obtained only by microscopic examination.

It is of interest and importance that benign tumors outnumber malignant tumors in a ratio of approximately 2 : 1.

The treatment is surgical excision.

ANOMALOUS FIXATION OF THE MESENTERY

REPORT OF TWO CASES

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ST. LOUIS

Anomalous fixation of the mesentery occurs fairly often. It varies from the rare primitive forms of embryonic fixation associated with nonrotation of the intestines to the common late forms of nonattachment of the mesentery of the ascending colon. Often no symptoms result, but sometimes symptoms arise owing to abnormal mobility of the ascending colon or to complications resulting from the mesenteric anomalies. Among possible complications caused by such anomalies are: intestinal obstruction caused by volvulus, intussusception or so-called internal hernia; obstruction caused by congenital peritoneal bands, and such complications as may arise from misplacement of the cecum and of the appendix.

The anomalies encountered after birth are believed to be due to arrests in fetal development. They fall naturally into one of the three stages into which fetal development has been divided by Frazer and Robbins,[1] by Dott [2] and by others. The present report deals only with the last of these stages.

Anomalies resulting from arrests in the third stage of intestinal development are more common than anomalies of the first or the second stage. They are, however, less striking, because they are characterized by a normal adult sequence of viscera, the intestines having fully developed and fully rotated; the resulting anomaly is simply one of failure of mesenteric adhesion to the posterior parietes. Anomalies of the third stage, moreover, are less likely to produce symptoms or complications necessitating surgical treatment. Consequently, they have received less consideration in the literature than have anomalies of the first and the second stages.

To appreciate the significance of such anomalies it is necessary to recall the course of intestinal development of the human fetus. This occurs, according to Frazer and Robbins [1] and Dott,[2] as follows: The primitive gut is divided by its blood supply into three parts, namely, the foregut, the midgut and the hindgut. The foregut is

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1. Frazer, J. E., and Robbins, R. H.: On the Factors Concerned in Causing Rotation of the Intestine in Man, J. Anat. & Physiol. **1**:75-110, 1915.

2. Dott, N. M.: Anomalies of Intestinal Rotation: Their Embryology and Surgical Aspects, with Report of Five Cases, Brit. J. Surg. **11**:251-286, 1923.

supplied by the vessels of the celiac axis and comprises the stomach and the duodenum. The midgut is supplied by the superior mesenteric artery and comprises the entire small intestine, together with the cecum, the appendix, the ascending colon and the transverse colon as far as its middle third. The hindgut is supplied by the inferior mesenteric artery and comprises the remainder of the transverse colon together with the distal part of the colon as far as the anal canal.

The midgut, because of its complex mode of evolution, is responsible for many developmental anomalies. It progresses, according to Dott, through three stages of rotation. The first stage of rotation occurs about the eighth week of development of the human embryo. The midgut, already possessing a mesentery with sagittal fixation of the root, is still attached to the yolk sac at the vitelline duct and protrudes through the umbilicus. It begins to rotate counterclockwise with the superior mesenteric artery as an axis, owing to the pressure of the left umbilical vein.

In the second stage of rotation the small intestine returns into the abdomen, posterior to the superior mesenteric vessels. Rotation occurs through an arc of 270 degrees in counterclockwise direction until the normal adult intestinal sequence has been attained. The cecum is the last part of the midgut to return to the abdominal cavity.

At the beginning of the third stage the intestinal sequence is the same as in the adult, but the cecum still lies high. Moreover, the midgut is still attached to a large common mesentery with a small root. During the third stage the cecum descends into the right lower quadrant of the abdomen, and the mesentery of the ascending colon adheres to the posterior parietes as far as the line of the superior mesenteric artery, thus forming the normal adult mesenteric root for the small intestines. The third stage occurs in the human embryo of about 63 mm., or at about the twelfth week of embryonic growth.

The hindgut retains some of its primitive mesentery until the third stage of development, during which the mesentery of the descending colon adheres to the posterior parietes.

Two instances of anomaly of the third stage of development were recently observed in cadavers. They were accidentally encountered during the routine dissection of 148 successive cadavers by students and instructors in the department of anatomy under the direction of Dr. Robert J. Terry.

REPORT OF CASES

CASE 1.—The cadaver was that of a Rumanian man who died in St. Louis City Hospital No. 1 on Nov. 3, 1930, at the age of 60. Death was due to chronic myocarditis and hypostatic bronchopneumonia. Dissection was performed in November 1931. The body was preserved by injection into the right femoral artery of solution of formaldehyde U. S. P. in a 10 per cent concentration. The state of preservation of the cadaver at the time of dissection was excellent. There was

no history of previous abdominal illness. There had been no operations, and the abdominal wall showed no scar. During the stay in the hospital the intake of food and fluid and the output of feces were in no way abnormal.

Figure 1 shows the viscera of the cadaver. For the drawing the mesentery was viewed from below. The small intestines and the right side of the colon possessed a common mesentery. The mesentery had a small root which was

Fig. 1.—Mobile cecum and intestines. The mobility resulted from faulty mesenteric fixation during the third stage of intestinal rotation. *D*, duodenum; *G Bl*, gallbladder. The arrow disappears into the epiploic foramen.

coextensive with the superior mesenteric artery. The superior mesenteric artery lay anterior to the third portion of the duodenum. The third portion and part of the second portion of the duodenum lay within the mesentery, as did the head of the pancreas. The mesentery was continuous with the mesentery of the transverse colon.

The right colic (hepatic) flexure was held to the gallbladder and the liver by peritoneal bands. The left side of the colon was unaltered, and the descending colon had no mesentery.

The attachment of the right colic (hepatic) flexure was interesting. Figure 2 shows the origin of a congenital peritoneal band from the inferior surface of the quadrate lobe of the liver, extending thence to the right colic flexure. The right colic flexure was supported by this congenital band. Additional support was furnished by adhesions between it and the gallbladder, which may not have been of congenital origin.

The hepatocolic ligament of this cadaver was thin and resembled peritoneum. It was about 5 cm. in width. It resembled certain accessory ligaments which are common in this region and which, according to Cole,[3] Wakefield and Mayo [4] and others, are of congenital origin.

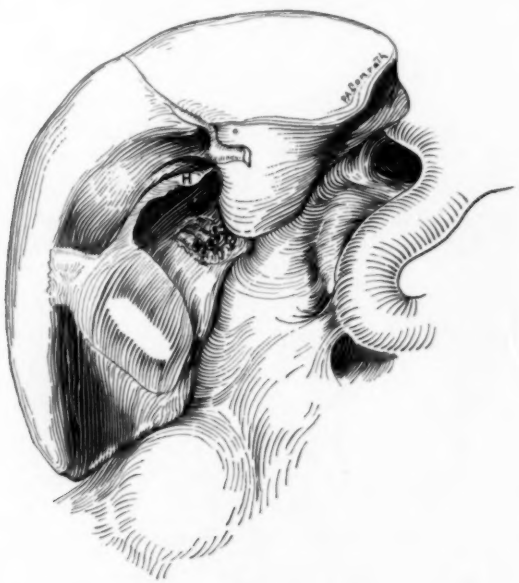

Fig. 2.—At *H* is shown the attachment to the liver of a congenital ligament running to the right colic flexure.

Had it not been for this method of fixation of the right colic flexure, the whole of the midgut of this cadaver would have hung from a small pedicle at the superior mesenteric artery and would have been especially liable to volvulus.

Figure 3 shows diagrammatically the peritoneal reflections of the posterior abdominal wall in this cadaver. The root of the mesentery lay at the level of the upper border of the body of the second lumbar vertebra. It was continuous above with the mesentery of the transverse colon, which was arranged

3. Cole, W. H.: Congenital Malformations of the Intestinal Tract and Bile Ducts in Infancy and Childhood, Arch. Surg. **23**:820-847 (Nov.) 1931.

4. Wakefield, E. G., and Mayo, C. W.: Intestinal Obstruction Produced by Mesenteric Bands in Association with Failure of Intestinal Rotation, Arch. Surg. **33**:47-67 (July) 1936.

in normal fashion. The descending colon was fixed to the posterior parietes in the usual fashion. The sigmoid flexure possessed a normal mesentery, and the relations of the rectum to the surrounding structures were unaltered. The omentum was normal. The vascular system of the abdomen was normal.

The cadaver showed several associated anatomic anomalies. The frontal bone possessed one metropic suture. There were double hypoglossal canals on both sides. The xiphoid process was bifurcate. The fifth lumbar vertebra showed separation of the inferior articular processes. Each femur had a large trochanter tertius. The second and third phalanges of the little toes of both feet were fused.

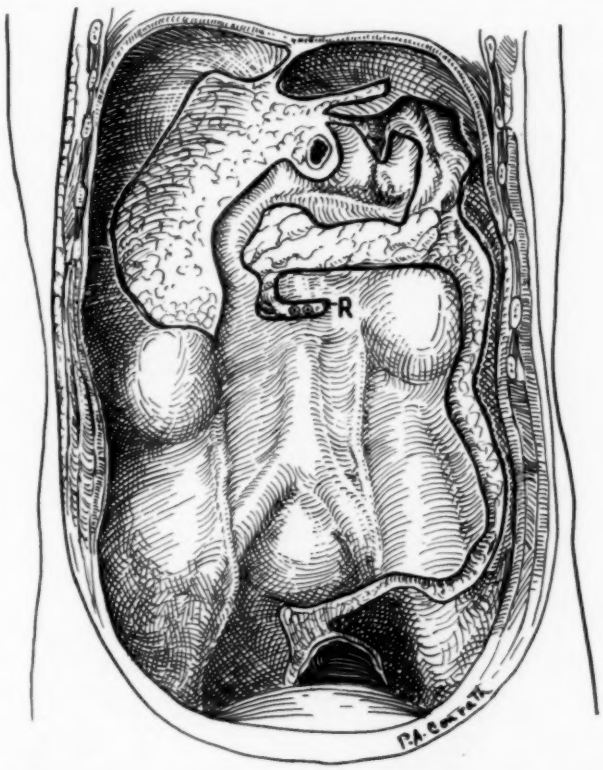

Fig. 3.—Semidiagrammatic drawing of the mesenteric root after removal of the preperitoneal viscera. *R*, root of the mesentery of the duodenum, the small intestines and the ascending colon. The root contains the superior mesenteric vessels and lies over the pancreas.

Case 2.—The cadaver was that of Mrs. M. R., a Negress aged 41, who died at St. Louis City Hospital No. 2 on Feb. 24, 1932, of carcinoma of the cervix uteri, complicated by pulmonary tuberculosis. There was nothing in the history of this patient to suggest congenital abdominal disease, and there were no abdominal scars. Dissection of this cadaver was performed in February 1933. The cadaver was preserved in solution of formaldehyde by a technic similar to that used with the previous cadaver. It was in good condition for dissection.

The cadaver possessed a primitive mesentery almost identical with that just described except that the right colic flexure was not attached to the liver. The

superior mesenteric artery lay anterior to the third part of the duodenum, at the level of the body of the second lumbar vertebra. Associated anomalies observed in this cadaver were as follows: (1) The posterior arch of the atlas was not united; (2) there were no parietal foramens in the calvaria; (3) the left humerus possessed an intercondylar foramen, and (4) the second and third phalanges of both little toes were fused.

COMMENT

Incidence.—These 2 cases illustrating failure of mesenteric fixation during the third stage of intestinal development were encountered in the course of dissection of 148 successive cadavers. The incidence of the anomaly in the series of dissections was 1.4 per cent. Treves [5] observed 2 similar anomalies during dissection of 100 bodies immediately post mortem, an incidence of 2 per cent. Waugh [6] reported a 20 per cent incidence of mesenteric anomalies in a series of several hundred autopsies on children under 12. However, all types of intestinal anomalies which caused mobility of the ascending colon were included in his series. Moritz [7] stated that "secondary attachments (of the mesentery) are incomplete in almost 25 per cent of all individuals."

Cause.—It is possible that certain mechanical forces may cause failure of mesenteric adhesion to the posterior parietes in the third stage of rotation. It was interesting to find in the cadaver in the first case a hepatocolic ligament which served to support the hepatic flexure of the colon and acted as an anchor for the entire mesentery. This ligament was believed to be of congenital origin. It resembled a congenital band which extended from the transverse fissure of the liver over the gallbladder and the second portion of the duodenum to the hepatic flexure in a case reported by Waugh.[8]

Congenital bands in the neighborhood of the duodenum are not uncommon. They were first described by Virchow in 1853, according to Wakefield and Mayo, and have been studied by Garnier and Villemin,[9] Latarjet and Tavernier [10] and others. They have been found associated

5. Treves, F.: The Anatomy of the Intestinal Canal and Peritoneum in Man, London, H. K. Lewis, 1885; Clinical Lecture on Hernia into the Foramen of Winslow, Lancet **2**:701, 1888.

6. Waugh, G. E.: The Morbid Consequences of a Mobile Ascending Colon with a Record of One Hundred and Eighty Operations, Brit. J. Surg. **7**:343-383, 1920.

7. Moritz, A. R.: Mesenterium Commune with Intestinal Obstruction, Am. J. Path. **8**:735-744, 1932; Developmental Anomalies Causing or Predisposing to Intestinal Obstruction, Ohio State M. J. **30**:429-433, 1934.

8. Waugh, G. E.: Congenital Malformations of the Mesentery: A Clinical Entity, Brit. J. Surg. **15**:438-449, 1928.

9. Garnier, C., and Villemin, F.: Ligaments hépatiques accessoires chez le foetus humain, Bibliog. anat. **20**:80-92, 1910.

10. Latarjet, A., and Tavernier, L.: Un cas de defaut d'accolement du mesentére primitif dans le territoire irrigué par l'artere mesenterique superieure, Bibliog. anat. **20**:93-96, 1910.

with failure of mesenteric adhesion to the posterior parietes with sufficient frequency to raise the question whether they may not be a cause of such failure. Cole concluded that congenital bands in the region of the duodenum are caused by incomplete absorption of the stem processes that support the liver and pancreas as they bud forth from the duodenum early in embryonic life. It is possible that such congenital bands may sometimes give enough mechanical support to the right side of the colon to prevent its full fixation to the posterior abdominal wall.

Another anomaly associated with failure of mesenteric adhesion in the third stage of intestinal rotation was the occurrence of a congenital foramen in the mesentery of the small intestine in a case reported by Moritz.[7]

Symptoms.—Waugh claimed that a mobile ascending colon often gives rise to symptoms and reported 180 operations for the cure of the condition. His work does not appear to have received confirmation, and an unusually mobile cecum is not generally thought to cause symptoms or to require surgical fixation.

Signs.—No abdominal physical signs arise from this type of anomaly per se. Such signs as may arise are due to the consequences of the anomaly, namely, to a malplaced appendix to volvulus or to intestinal obstruction. A diagnosis by roentgen examination is possible. The right half of the colon may be seen to gravitate to the right or to the left of the abdomen, according to the position of the patient and the manipulation of the right half of the colon. If normal adult sequence of intestines is not present the anomaly is probably one of the first or second stage, not the third.

Diagnosis.—At operation it is of more than theoretic importance to recognize this anomaly. The diagnostic point is the relation of the duodenum to the superior mesenteric artery. If the duodenum lies posterior to the artery in the presence of deficient mesenteric fixation, the anomaly is one of the third stage of development, because counterclockwise rotation of the intestines through an arc of 270 degrees has occurred in normal fashion. However, if the duodenum lies anterior to the superior mesenteric artery the anomaly is one which has resulted from defective rotation in the second or the first stage, and the normal adult sequence of intestines cannot be expected. These points are of practical importance in the reduction of volvulus which may have occurred from an intestinal anomaly. Volvulus always occurs in clockwise direction.

Roentgen diagnosis of anomalies of intestinal rotation has been discussed by Rubin.[11]

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11. Rubin, E. L.: Radiological Aspects of Anomalies of Intestinal Rotation, Lancet **2**:1222-1226, 1935.

Sequelae.—Failure of mesenteric adhesion in the third stage of rotation results in a freely movable cecum, or cecum mobile. It is possible, in consequence of this mobility, for the appendix to migrate to any quadrant of the abdomen. The potentialities in the nature of atypically located appendicitis are obvious.

Cases in which the anomaly has resulted in intestinal obstruction have been recorded by Moritz. In 1 of his cases the obstruction was due to a volvulus of the small intestine and the right half of the colon about the superior mesenteric artery. The result was obstruction at the third portion of the duodenum, and the patient died after the operation, not from this obstruction but from another unrelieved obstruction of the small intestine in a congenital foramen in the mesentery, not recognized at the time of the original operation. Ladd [12] has discussed duodenal obstruction in infancy and in childhood caused by this and by other anomalies. Another patient of Moritz' had intussusception of the terminal part of the ileum into the cecum as a result of the anomaly.

In 3 cases reported by Pratt and Fallis [13] the patients had intestinal obstruction from cecum mobile.

Anomalies of the third stage of intestinal rotation seem to be well tolerated and to be associated with relatively few morbid sequelae. Morbid sequelae occur much more often from anomalies of the first and second stage of intestinal rotation. The articles of Haymond and Dragstedt [14] and of Gardner and Hart [15] summarized the present status of these anomalies.

SUMMARY

Two cases illustrating developmental anomalies of the third stage of intestinal rotation are presented. Apparently neither anomaly caused symptoms during life, and both were discovered accidentally post mortem, during routine dissection. The 2 cases were observed in the course of dissection of 148 successive cadavers.

Evidence is presented to confirm the belief that this type of anomaly occurs in over 1 per cent of adults. It is probably unrecognized as a rule because it fails to cause symptoms. Owing to its presence, however, the cecum becomes mobile and the appendix becomes liable to malposition. Sequelae, i. e., different forms of intestinal obstruction, have been reported.

12. Ladd, W. E.: Congenital Obstruction of the Duodenum in Childhood, New England J. Med. **206**:277-283, 1932.

13. Pratt, J. P., and Fallis, L. S.: Volvulus of the Cecum and Ascending Colon: Report of Three Cases, J. A. M. A. **89**:1225-1230 (Oct. 8) 1927.

14. Haymond, H. E., and Dragstedt, L. R.: Anomalies of Intestinal Rotation: A Review of the Literature with Report of Two Cases, Surg., Gynec. & Obst. **53**: 316-329, 1931.

15. Gardner, C. E., Jr., and Hart, D.: Anomalies of Intestinal Rotation as a Cause of Intestinal Obstruction, Arch. Surg. **29**:942-981 (Dec.) 1934.

PRIMARY CARCINOMA OF THE NAIL

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AND
JAMES R. LISA, M.D.
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Neoplasm arising from the nail is one of the rarest manifestations of malignant disease. A careful search of the literature reveals only 17 proved cases and 1 probable case. Carcinoma of the nail develops, according to Pardo-Castello,[1] from the epithelium of the bed, the matrix or the nail grooves and is usually of the prickle cell type. An additional case is here reported.

REPORT OF CASE

A white man aged 65 came to the outpatient department of the City Hospital on May 25, 1936, complaining of pain in the left great toe. The nail along the mesial side resembled an ingrowing nail and was treated accordingly but failed to improve. Three weeks later part of the nail was removed, and a warty growth beneath it was revealed. Eleven days later, block anesthesia being employed, the mass was further exposed and apparently entirely removed. The tissue was not submitted for histologic examination. Pain persisted and was accompanied by swelling, redness and tenderness. On August 28 an abscess-like cavity was present which could be probed to the bone. The discharge was described at various times as sebaceous or caseous. Roentgen examination showed lateral hypertrophic exostosis and destruction of the terminal phalangeal bone. A diagnosis of chronic osteomyelitis was made, and the patient was admitted to the hospital on September 10. Five days later the distal phalanx was amputated through the interphalangeal joint.

The pathologic report stated: "The specimen consists of a left great toe amputated through the interphalangeal joint. The nail had been cut diagonally, exposing the mesial portion of the subungual tissue, which appears heaped up and granular. On sagittal section of the toe, an ovoid mass near the tip is noted, immediately beneath and connected with the nail bed. This mass measures 1.5 cm. in length and 1 cm. in width. It grows toward the plantar surface and has destroyed the tip of the bone of the distal phalanx. It is firm, elastic, white and well demarcated from the surrounding tissue. The nail appears thicker than normal.

"Histologic structure: The tumor mass grows down from the nail bed and is formed by the coalescence of long pegs of squamous epithelium. Toward the center the cells are large polyhedral cells, sometimes flattened into platelike structures. The nuclei here are relatively small and vesicular. There is a definite tendency to intraepithelial keratinization, and some typical epithelial pearls are present. Intercellular bridges are prominent. Many foci are rich in keratohyaline granules. At the periphery of the mass the cells are compressed and are smaller

From the Department of Pathology, City Hospital.

1. Pardo-Castello, V.: Diseases of the Nail, Springfield, Ill., Charles C. Thomas, Publisher, 1936, pp. 47-50.

than toward the center. The nuclei are fairly large and moderately hyperchromatic, with fairly large nucleoli, and there is an occasional mitotic figure. In a few areas there is destruction of the basal limiting membrane, and isolated epithelial

Fig. 1.—Amputated toe, showing the granular appearance of the subungual tissue revealed by partial removal of the nail.

Fig. 2.—Sagittal section of the toe. The tumor mass has grown down from the under surface of the thickened nail and has destroyed the tip of the phalangeal bone.

cells are present in the adjacent connective tissue. The central portion of the tumor has large defects which communicate with the heaped-up granular area noted on the surface of the gross specimen. This area is similar to the main tumor mass, and some portions show a definite transition to nail-plate cells.

"Near the edge of the tumor the epithelium of the nail bed becomes increasingly acanthotic. In the corium there is dense infiltration with small round cells, plasma and lymphoid cells predominating in different foci. There is a scattering of eosinophilic cells. The tumor mass has destroyed by pressure the tip of the phalangeal bone. The periosteum adjacent to the tumor shows slight productive changes, and the underlying marrow spaces are fibrotic. Some young osteoid lamellae are being formed. The majority of the bone shows osteoporosis. Malignant cells have not invaded the bone itself.

"The diagnosis is primary squamous cell carcinoma of the nail of the left great toe, originating from the nail bed."

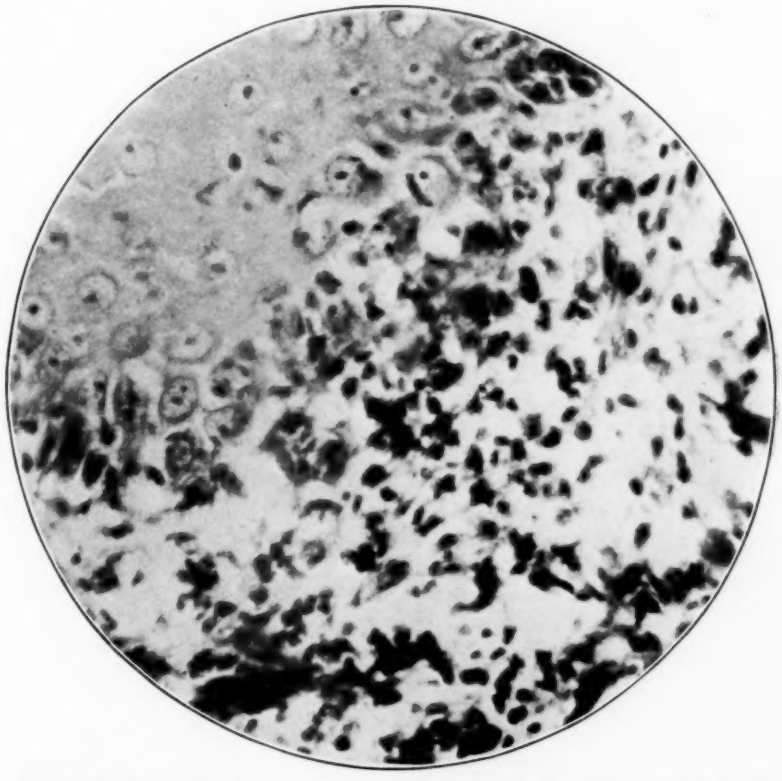

Fig. 3.—High power photomicrograph of the edge of the tumor, showing local invasion by malignant epithelial cells. There is dense small round cell infiltration.

COMMENT

The accompanying table summarizes the salient features of the previously reported cases. In the total 19 cases (including our own), 11 patients were males, 7 were females and the sex of 1 was not noted. The ages varied from 21 to 75. Ten of the patients had a definite history of injury, often followed by chronic infection, preceding the frank development of malignant tumor. The period from the time of injury to the time malignant tumor was diagnosed was given in some cases and

Previously Reported Cases of Primary Carcinoma of the Nail

Case Number and Author	Sex	Age	Antecedent Condition	Injury	Duration*	Site	Treatment	Result	Histologic Structure
1. Velpeau, M.: Gaz. d. hôp. **2**: 314, 1850	F	61	Occupational use of chemical solutions for several years	Puncture wound	1 yr.	Right index finger	Amputation	Cure	Epithelioma
2. Küster [3]	M	34	Ingrowing nail	Injury followed by chronic painful paronychia	6 mo.	Right thumb	Amputation	Cure	Squamous cell carcinoma
3. Lücke, cited by Rokoch, C.: Ueber die chirurgischen Affektionen des Nagelgleids, Thesis, Bonn, 1889	M	65	None	Yes	.....	Right thumb	Amputation	Cure	Carcinoma
4. Robin: Bull. Soc. anat. de Paris **48**: 42, 1873	F	21	None	None	11 yr.	Right index finger	Amputation	Cure	Epithelioma
5. Krönlein [3]	M	44	None	Crushing injury followed by painful scar	1 yr.	Right little toe	Amputation	Died†	Carcinoma
6. Hutchinson [4]	M	70	Purulent discharge	None	10 yr.	Thumb	Amputation	4 yr. cure	Epithelioma
7. Toupet: Bull. Soc. anat. de Paris **64**: 30, 1889	F	35	.....	None	.....	Great toe	Amputation	Cure	Epithelioma
8. Kolliker, cited by Volkmann: Samml. klin. Vortr., 1890 (Chir. no. 102), p. 3123	..	..	Ingrowing nail with chronic paronychia	.....	.....	Great toe	Amputation	.....	Carcinoma
9. Peyrot, cited by Heller, J.: Diseases of the Nails, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol. 13, pt. 2, p. 168	F	48	.....	.....	.....	Right index finger	Amputation	Cure	Carcinoma
10. Blakeway, H.: St. Barth. Hosp. Rep. **46**: 193, 1910	M	50	Loose nail and purulent discharge	None	1 yr.	Right thumb	Refused	.....	Squamous cell carcinoma
11. Heidingsfeld, M. L.: Lancet-Clinic **113**: 583, 1915	M	60	None	Injury followed by indolent ulcer	10 yr.	Right thumb	Radium	Cure	Clinical diagnosis of epithelioma; no histologic exam.
12. Chagas [5]	M	60	None	Yes	18 yr.	Right great toe	.....	.....	Carcinoma
13. Eisenklam, D.: Wien. klin. Wchnschr. **44**: 1192, 1931	F	20	.....	.....	.....	Left great toe	Removal of nail	.....	Papilloma with early malignancy
14. Eisenklam	M	50	None	Yes	.....	Middle finger	Removal of nail	.....	Basal cell carcinoma
15. Réchou and others: Bull. et mém. Soc. de radiol. méd. de France **20**: 232, 1932	M	66	.....	Puncture wound under nail	.....	Right thumb	Radium	Cure	Basal cell carcinoma
16. Silverman, I.: Am. J. Surg. **29**: 141, 1935	F	70	.....	Injury followed by chronic paronychia	2½ yr.	Right thumb	Roentgen therapy	Local recurrence	Squamous cell epithelioma
17. Pardo-Castello [1]	M	50	.....	Splinter under nail; suppuration 3 years later	4 yr.	Thumb	Radium	Cure	Prickle cell epithelioma
18. Pardo-Castello [1]	F	75	Bowen's disease	.....	.....	Middle finger	.....	.....	Prickle cell epithelioma

* Time given is between onset of symptoms and time of diagnosis.
† Metastases to inguinal lymph nodes, gangrene of leg and death following surgical removal of nodes.

varied from six months to eighteen years. The type of trauma, infrequently noted, was in 3 cases a deep puncture wound between the nail and the nail bed; in 1 case it was a crushing injury.[2] Infection, when present, was resistant to treatment. In 3 cases the carcinoma followed paronychia. In 2 of these cases paronychia followed injury, and in 1 of these there was an ingrowing nail; an ingrowing nail was also present in the case of nontraumatic paronychia. In 1 case the carcinoma followed Bowen's disease, a condition sometimes considered precancerous. The history of trauma seems to explain the sites of predilection; the lesions occurred in those parts which are most subject to injury. Thus, in 13 cases the hand was affected, and in 9 of these the diseased digit was the right thumb or index finger. Of the 6 tumors involving the foot, all were on either the great or the small toe.

Pain was noted as a prominent symptom in 7 cases. From the slowly expanding nature of the lesion and its limitation by the rigid nail and by phalangeal bone it seems probable that pain was present in some of the other cases also.

In the case here reported there was a discharge described as sebaceous or caseous. This probably represented an actual discharge of cancer tissue and might have been of some diagnostic value.

The most frequent histologic diagnosis was squamous cell carcinoma. There were 2 cases of basal cell carcinoma and 1 of papilloma with early malignant degeneration. Pardo-Castello stated that carcinomas of the nail are rather malignant, but in our review of the cases the malignancy appears to be of a low grade. In only 4 cases, including our own, was mention made of the presence or absence of involvement of bone. In 1 case [3] there was no involvement of the bone. In our own case and 1 other [4] there were erosion and atrophy of bone, caused by pressure rather than by invasion. In only 1 case [5] was there true local invasion of bone. Metastases from carcinoma of the nail are infrequent, if one may so infer from the fact that they are seldom mentioned. In a single instance only were the draining lymph nodes involved.

The treatment has been amputation, excision of the nail and radium or roentgen therapy. The results seem to have been uniformly good, except for 1 case in which there were metastases to the lymph nodes and 1 case of local recurrence after administration of roentgen therapy.

* Time given is between onset of symptoms and time of diagnosis.
† Metastases to inguinal lymph nodes, gangrene of leg and death following surgical removal of nodes.

2. Krönlein, R. W.: Langenkeck'sche Klinik und Poliklinik zu Berlin: Extremitäten; Geschwülste, Arch. f. klin. Chir. (supp.) **21**:336, 1877.

3. Küster, E.: Chirurgisch-onkologische Erfahrungen, Arch. f. klin. Chir. **12**:629, 1871.

4. Hutchinson, J., Jr.: Epithelioma of the Nail, Tr. Path. Soc. London **36**:468, 1885.

5. Chagas, C. P.: Carcinoma of the Matrix of the Nail of the Great Toe, Brasil-med. **35**:233, 1921.

SUMMARY AND CONCLUSIONS

The literature on carcinoma of the nail is reviewed, and an additional case is reported. Many of the neoplasms develop after trauma followed by chronic infection. The site of predilection corresponds with the fingers and toes most subject to injury, the right index finger and thumb and the great and little toe. The neoplasm usually is a squamous cell carcinoma and is of a low grade of malignancy. Local recurrence and metastases are very infrequent. Cure usually results from amputation or radium therapy.

A PLASTIC OPERATION ON THE BREAST

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PHILADELPHIA

Plastic operation on the breast is a recent addition to plastic surgery. This new field owes some of its demand to the importance that women of today attribute to a properly proportioned form. Vogues and sports have given rise to comparisons which make a woman conscious of having a normal or an abnormal form. Therefore, hypertrophic and pendulous breasts, which in moderate degrees are fairly common, may constitute a psychic handicap. For a small group of women with enormously heavy breasts, there is added to the psychic handicap a physical one, and the two may constitute a tragedy of life, since they frequently occur in young women with otherwise slim figures. When it is possible safely and satisfactorily to correct a deformity of the breasts and thus to restore the happiness of a patient, plastic reconstruction of the breast is a justifiable operation.

Surgeons distinguish an atrophic pendulous breast from a hypertrophic one. In the former, the breast is a flabby sac of skin containing scanty breast tissue at its bottom. In the hypertrophic form, the enlargement of the breast is due to overdevelopment of its tissue and consists of glandular tissue and fat.

The reconstructive operation for a pendulous breast has a twofold purpose: first, that of correcting the deformity and, secondly, that of maintaining the function of the gland. To accomplish these aims, several operative methods, which have recently been described by Maliniak [1] and by Biesenberger,[2] have been devised. Biesenberger has divided the different operations into four groups—partial amputation, mastopexy, dermatoplasty and dermatoplasty plus resection. The first method is performed nowadays only in exceptional cases, since it is always combined with a separation of the nipples from the glandular tissue and therefore with loss of function. Mastopexy and the various

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Read before the Philadelphia Academy of Surgery, Jan. 3, 1938.

From the service of Dr. George P. Müller at the Lankenau Hospital.

1. Maliniak, J. W.: Pendulous Hypertrophic Breast, Arch. Surg. **31**:587 (Oct.) 1935.

2. Biesenberger, H.: Deformitäten und kosmetische Operationen der weiblichen Brust, Vienna, Wilhelm Maudrich, 1931.

methods of dermatoplasty have a limited scope, as they do not decrease the size of the breasts. When the operation of resection and displacement of the nipples to their natural places was devised, however, a reliable method was afforded of reconstructing pendulous breasts into natural forms without disturbing function.

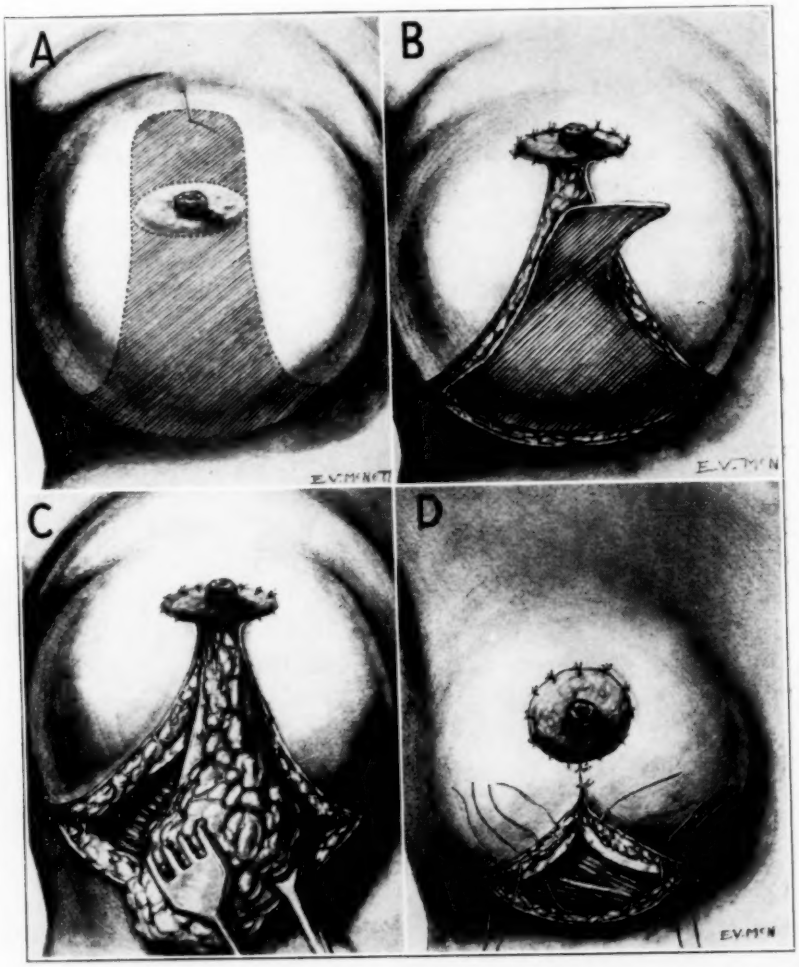

Fig. 1.—*A*, the place to which the nipples are to be transferred is marked with a pin; the areola is circumscribed by an incision and the parts of skin to be resected are outlined. *B*, the skin above the areola is excised; the areola is lifted and sewed into the upper corner of the defect; the skin beneath the areola outlined by the previous incision is partly detached. *C*, the skin beneath the areola is excised; the hypertrophic breast tissue is removed. *D*, the wound is closed in layers; the lower edge of the breast is anchored to a bridge flap of the major pectoral muscle.

Lexer,[3] as far as can be ascertained, was the first to devise this method. His operation, which I am adopting, might be described as follows: After the usual preparation and with the patient under complete anesthesia, the two points to which the nipples are to be transferred are marked with a pin, so that comparison as to normal position and correlation can be made (fig. 1 *A*). The areola of one side is then circumscribed by an incision, and above this is excised a piece of skin of the same width as the areola and with a rounded end as far above the pin as the nipple is distant from the margin of the areola. After this excision, the skin beneath the areola is incised in continuation of the upper cuts, not parallel, but in diverging curves, so that the terminal parts of the incisions lie within the fold of the breast. An incision running along this fold completes the outline of that part of the skin which is to be excised later. The areola is then lifted and sewed into the upper corner of the defect (fig. 1 *B*). The hypertrophic part of the breast now bulges below the areola. The skin beneath the nipple, which was outlined by the previous incision, is next excised. The bulging fatty tissue is now grasped and excised along the edge of the skin and is separated from the pectoral fascia (fig. 1 *C*). After the bleeding is checked, the wound is closed in layers (fig. 1 *D*). The first suture approximates the edges of the wound just below the nipple with a bite through the pectoral fascia. To support the breast from below, a bridge flap of the major pectoral muscle is lifted at the lower edge of the breast. The last suture through the breast tissue is also passed through this flap of muscle. Finally, the skin is closed.

In the case of atrophic breasts, the operation is the same, with the one exception that no breast tissue is excised; the tissue is merely inverted with mattress sutures to erect the breast.

The operation should be done on both sides at one sitting. In most cases, it can be performed in one stage. In cases of unusually large breasts, however, a two stage operation is safer in order not to endanger the nipple.

The cases of 2 patients operated on by me may be mentioned here as examples. The first patient had hypertrophic pendulous breasts of moderate degree (fig. 2). In the second patient the hypertrophy of the breasts was more pronounced (fig. 3). For both patients a one stage operation was employed.

The advantage of this method of plastic operation on the breasts outlined herewith is threefold: 1. Since the planes of the wound curve outward and broaden below, the breast, after approximation of the edges of the wound, becomes erect and pointing rather than flat. 2. The scars,

3. Lexer, E.: Die gesamte Wiederherstellungschirurgie, Leipzig, Johann Ambrosius Barth, 1931.

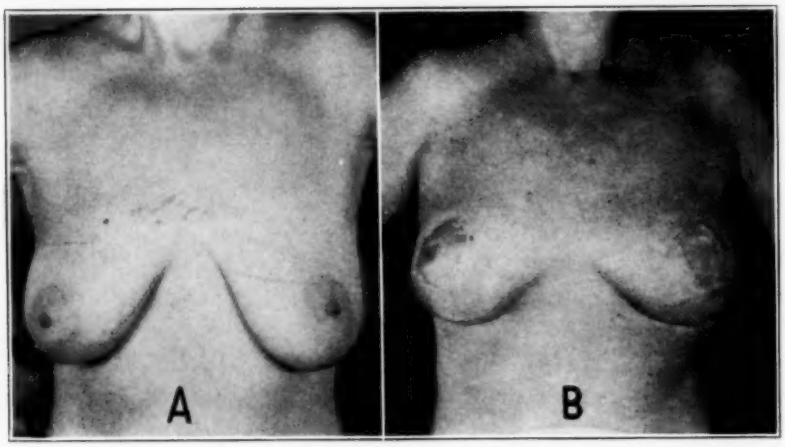

Fig. 2.—*A*, hypertrophic pendulous breasts of moderate form. *B*, same patient five weeks after plastic repair.

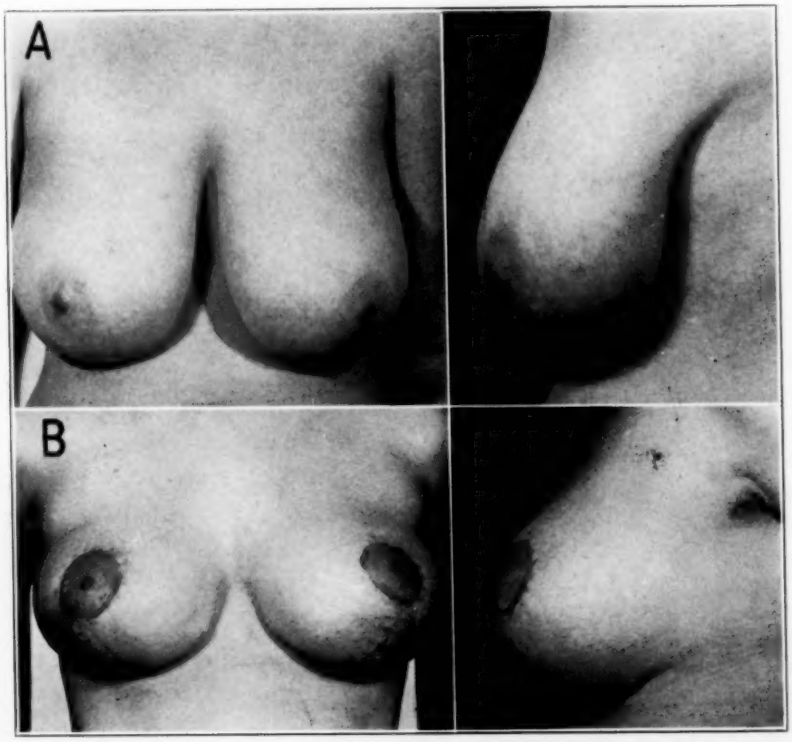

Fig. 3.—*A*, the more pronounced form of hypertrophic pendulous breasts. *B*, the same patient three weeks after plastic operation.

which usually disappear after three months, are situated in the lower half of the breast and in the submammary fold. 3. The function of the gland is not disturbed. On the latter point I have had no experience in my own practice, but I have seen several examples among Lexer's patients.

SUMMARY

Plastic operation on the breasts is more in demand today because of the importance which women attribute to a properly proportioned form. This operation is described in detail, according to Lexer's technic, and two examples are given.

USE OF THE CUTIS GRAFT IN PLASTIC OPERATIONS

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ROCHESTER, MINN.

A review of the literature on the use of skin in certain types of plastic operations reveals that it has been suggested for application. No reports of conclusive experimental or clinical studies with this easily available autoplastic material have appeared except those articles which have been published in the German literature.

Professor E. Rehn has successfully used this material, which he and Loewe called the cutis graft, in plastic operations. The gratifying results seem worthy of consideration.

To avoid any misunderstanding, it is advisable first to define the term "cutis."

This word was coined by those who suggested the use of this type of skin graft because, though it is derived from the skin, it is not a bona fide skin graft. It does contain the cutaneous and subcutaneous structures of skin, but it is devoid of its epidermal covering when it is transplanted.

The employment of cutis in plastic operations was first advocated by Rehn [1] and Loewe [2] prior to 1914. Rehn, however, first applied it clinically in the treatment of postoperative hernia in cases in which the anatomic structures had been weakened to such an extent by the operation that a plastic repair was required to prevent recurrence. The results in these cases were so encouraging that gradually in the past nine years the field of application has been broadened to include twelve types of surgical conditions in which the cutis transplant was successfully used. In this article some of the experiments which led up to the clinical application of the results will be briefly outlined. This outline will be followed by a description of the operative procedures and by an analysis of the results obtained in the 104 cases in which plastic operations with cutis have been performed in Rehn's clinic since 1928.

Rehn concluded that cutis is the most suitable material for repairing defects because it best answers the requirements for tissue regeneration,

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The work reported here was done in the University Surgical Clinic (Professor E. Rehn), Freiburg, Germany.

1. Rehn, E.: München. med. Wchnschr. **1**:118, 1914. Rehn, E., and Miyauchi: Arch. f. klin. Chir. **105**:1, 1914.
2. Loewe, O.: München. med. Wchnschr. **24**:1320, 1913.

as outlined by Roux [3] in 1912. Cutis contains all the components of the skin except the epidermis; it is elastic; it is inherently active; and it is composed of a rich network of connective tissue fibers. After its transplantation these inherent factors assist in the metamorphosis of the graft. Owing to the stimulus set up by the tension under which the graft has been sewn, a gradual metaplasia of the transplant takes place. The inherent activity of the graft accelerates repair by encourging immigration of the cellular elements. Fascia, since it is inactive, acts only as a conductor of the migrating cellular elements, Rehn stated. Because of its histologic structure it can permit regeneration only in two planes at right angles to one another.

Rehn [4] and Schwartz [5] in experiments on dogs performed a tenotomy of the achilles tendon and closed the defect with a cutis graft. Under the influence of the functional *Reiz* elicited by their procedure of fixation of the graft to the tendon stumps, a gradual metamorphosis of the cutis into a tendon difficult to differentiate from a normal tendon occurred in about ten weeks. Transplanted fascia regenerated more slowly and failed to repair as well. The explanation lies in the inherent activity and longevity of cutis.

Eitel [6] showed rather conclusively that cutis lives longer and is more active than fascia and therefore is more suitable for plastic repair. He removed pieces of human fascia and cutis at operation and performed metabolic studies on them with the Warburg technic. In the accompanying chart (fig. 1) will be found his evidence of the superior viability of cutis as compared with fascia. Eitel stated that it holds for all age groups.

Schneider [7] found that cutis, like the other tissues which tend to regenerate most satisfactorily, contains no reduced glutathione. He selected reduced glutathione to exemplify a product of tissue oxidation and reduction. He analyzed the reduced glutathione content of various tissues to determine the role played by this substance in the ability of tissue transplants to grow. He found also that tissues which do contain this reduced substance regenerated poorly when transplanted, according to the amount found in them (table 1).

Histologic proof of the activity and the resulting metamorphosis of the cutis transplant was afforded me by the unexpected return of 2 patients on whom cutis operations had been done four years previously.

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3. Roux, W.: Terminologie der Entwicklungsmechanik der Tiere und Pflanzen, Leipzig, Wilhelm Engelmann, 1913.

4. Rehn, E., (*a*) in Lexer, E.: Die freien Transplantationen, Stuttgart, Ferdinand Enke, 1924, pt. 2, p. 503; (*b*) cited by Benninghoff: Verhandl. d. anat. Gesellsch. **40**:95, 1931; (*c*) Arch. f. klin. Chir. **186**:244, 1936.

5. Schwartz, E.: Deutsche Ztschr. f. Chir. **173**:301, 1922.

6. Eitel, H.: Deutsche Ztschr. f. Chir. **242**:806, 1934.

7. Schneider, E.: Arch. f. klin. Chir. **186**:267, 1936.

Pieces of tissue were removed from the healed cutis transplant area. Histologically the preparations presented normal connective tissue with its fibrous and fatty components containing their own blood and nerve supply. The abundant vascularity of the tissues was striking. No epidermal remnant of the original cutis graft and no dermoid cysts could be identified. Occasionally large cells with rather large nuclei, deep staining (with hematoxylin and eosin) and lying in rows or in rings were found (fig. 2).

These large cells might be interpreted as remnants of the hair follicles or the sweat glands of the original cutis graft or as macrophages produced by suture material reaction. Cameron,[7a] of Edinburgh, who

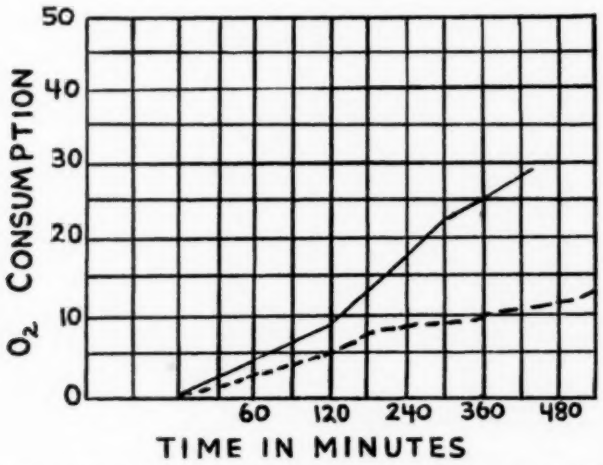

Fig. 1.—Superior viability of cutis as compared with fascia. The solid line represents cutis; the broken line, fascia.

TABLE 1.—*Relation of Gluthathione Content to Transplant Take (Schneider)*

	Reduced Glutathione Content	Outlook for Free Transplantation
Liver	+++	.....
Kidney	++	.....
Adrenal	++	.....
Thymus	++	.....
Muscle	++	.....
Heart	++	.....
Thyroid	+	Only temporary
Testis	+	Only temporary
Blood	.....	Only temporary
Bone	.....	+++
Fascia	.....	+++
Cutis	.....	+++
Tendon	.....	+++
Fat	.....	+++

7a. Personal communication to the author.

has been doing some experimental skin transplantations with guinea pigs, found similar histologic changes postoperatively but was unable to explain their cause. Besides these large cells, round cell infiltration with interspersed giant cells in a rather compact and well defined network of fibrillary connective tissue was found. No scar tissue was seen.

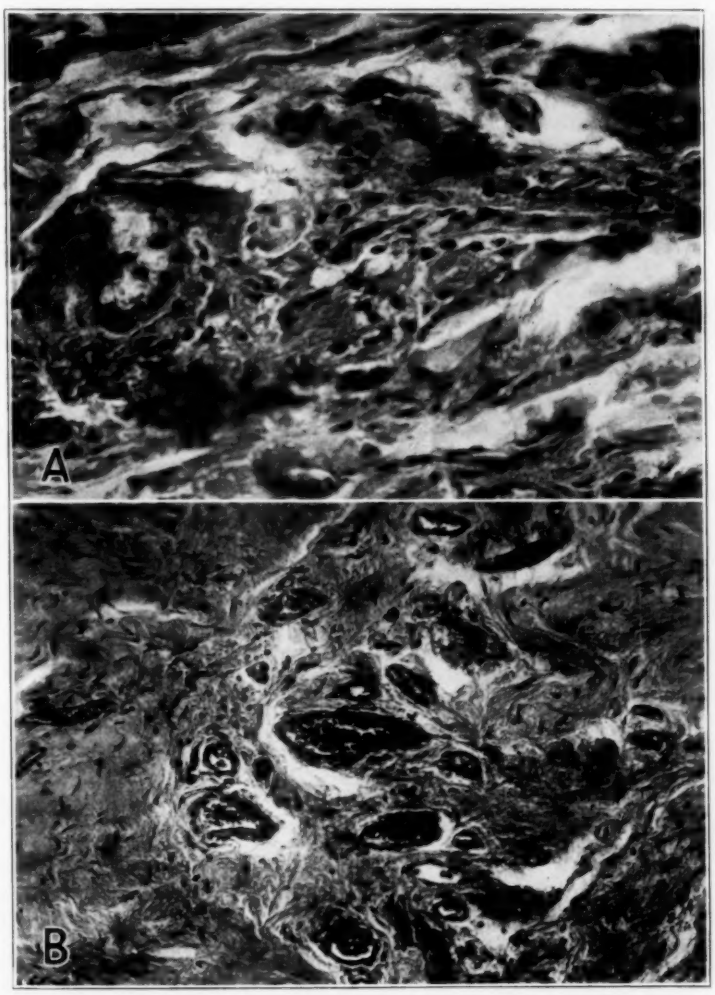

Fig. 2.—*A*, microscopic cross section of tissue excised from an area of previous cutis graft, showing large cells with deep-staining nuclei. *B*, microscopic cross section of the same tissue, showing its rich vascularity and viable connective tissue. No scar tissue is found.

Rehn applied the principles derived from his experimental findings to the plastic repair of human tissues. His first operations comprised the repair of large postoperative abdominal hernias with relaxed skin

and subcutaneous structures, the repair of which by any other form of operative procedure was not assured. Since 1928, 65 patients with hernia have been operated on by him or his assistants, with encouraging results. Sixteen patients failed to reply to a questionnaire sent them and to appear for reexamination. Of the remaining 49, 6 presented recurrences from two to nine years after operation. A ventral hernia before operation and abdominal and thigh wounds after the cutis repair are shown in figure 3. This patient had no recurrence of the hernia

Fig. 3.—*A*, preoperative lateral view of a large postoperative ventral hernia. *B*, anterior view of the patient eight weeks after a cutis graft operation, showing the well healed abdominal scar. *C*, lateral view of the patient, showing good abdominal support and a well healed scar on the thigh at the site from which the graft was removed.

seven years after the cutis plastic repair, despite the relaxed condition of all the abdominal muscular structures before operation.

Gradually the cutis transplant became the tissue of choice for other plastic operations, and to date Rehn has used it successfully in the thirteen different types of cases listed in table 2.

Before discussing the results obtained in the various types of cases in which cutis plastic procedures were employed, the manner in which the cutis is obtained and the prerequisites of a good result will be described. The transplant is usually taken from the lateral side of the thigh. This area, as well as the operative field, is thoroughly cleansed with compresses soaked in 70 per cent alcohol. These are applied daily five to eight days before operation for ward patients and one to four days before operation for private patients. A dressing soaked in a 3 per cent concentration of solution of formaldehyde U. S. P. in alcohol is generally substituted daily for ten minutes to insure better cleansing of the skin. On the day of operation both areas are washed for ten minutes with soap and water and then sponged off with 75 per cent alcohol and draped. No iodine should be used in preparing the area from which the graft is to

TABLE 2.—*Summary of Cutis Operations with Their Results*

Condition	Number	Results Good	Results Poor	Results Unknown
Postoperative hernia	65	43	6	16
Ventral hernia	4	3	..	1
Inguinal hernia	11	8	3	..
Knee joints with lateral motion	8	6	2	..
Habitual dislocation of jaw	1	1	..	..
Chronic dislocation of finger	1	1	..	..
Muscle hernia	2	1	1	..
Ruptured biceps tendon	3	2	..	1
Chronic laceration of extensor tendon	3	2	..	1
Habitual patellar luxation	3	2	1	..
Arthroplasty (elbow joint)	1	1 (for 3 yr.)	..	..
Fascia lata rupture	1	..	1	..
Mammary hypertrophy	1	..	..	1
Total	104	70	14	20

be taken. The desired piece of cutis is not excised until the major portion of the operation has been completed and the muscle groups clearly exposed for good fixation. For obtaining the graft the epidermis is first removed as completely as possible by the Thiersch method. This gives a fresh bleeding surface and minimizes infection. From the area free of epidermis an oval piece of cutis similar in size to the area to be covered or supported is excised to include about 1 cm. of fatty tissue (fig. 4).

The graft is placed in warm saline solution as the edges of the thigh wound are approximated with a running silk suture. After it has been made certain that hemostasis is complete in the area to which the graft is to be sewn, the cutis is placed over the defect. It is then sutured under tension at its upper and lower poles with chromic catgut to the generously exposed muscles and fascia (fig. 5). The graft is next stitched in its entire circumference to the surrounding exposed healthy tissues. It is stretched as much as possible after all the sutures have been securely fixed so that it resembles a taut drumhead. The skin and

subcutaneous tissues of the wound are then easily approximated over the graft, and the wound is closed in the usual manner.

These are the procedures usually carried out in Rehn's clinic for obtaining the transplant and suturing it to the area requiring repair.

Fig. 4.—Area of the thigh, free of epidermis, from which an oval piece of cutis of the desired dimensions may be excised.

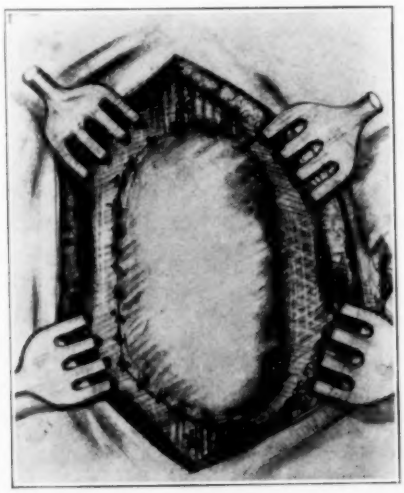

Fig. 5.—Schematic representation of the cutis graft after it has been fixed under tension to the exposed healthy tissues.

For cases in which an abdominal hernia is present and a cutis repair is necessary Rehn developed another operation, known as the "double-breasted vest" or "Türflügel" operation. In this procedure a flap is fashioned from the skin of the abdominal wall and is used as the cutis

graft (fig. 6). This type of operation has its limitations, since inelastic subcutaneous tissues and scarred skin are contraindications to its use. When the patient presents indications for this operation, one half of the incised skin area *abde* (fig. 6 *A*) is used as the cutis flap. After the epidermis has been removed, this flap is excised along the hypothetic line *ad* and is then fixed under good tension over the first stage hernia repair (fig 6 *C*). The opposite skin flap now closes the wound. Rehn has performed only 6 operations of this type in selected cases, with good results in 4 of them. Either of the aforementioned procedures is suitable for the repair of abdominal hernia, but the success of all plastic opera-

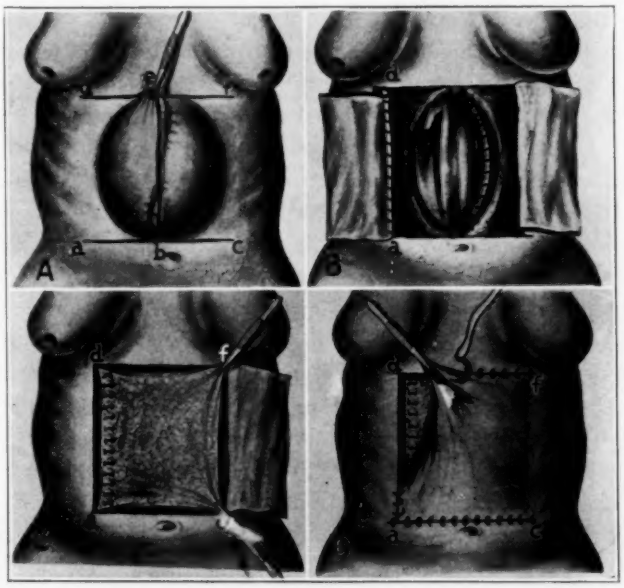

Fig. 6.—*A*, line of incision forming the two flaps used in the "double-breasted vest" operation for repair of ventral hernia. B, cutis flap fashioned from the flap *abde* and fixed with the first row of sutures. *C*, manner in which the cutis graft is sewn, under tension, over the repaired hernial sac. *D*, final closure of the wound. The anterior flap of skin is sutured over the buried cutis graft. (After Rehn.)

tions with cutis lies in the amount of tension under which the cutis is sewn over the defect. Without this tension the graft does not take satisfactorily.

The tension and pressure evoke the functional stimulus necessary to produce the metaplasia and metamorphosis. Likewise, in such repairs it is essential that a careful dissection with exposure of the muscles and fascia be made, so that accurate and supportive sutures can be placed to maintain the necessary degree of tension.

As was remarked earlier in this article, the cutis operation gradually became the procedure of choice for other conditions requiring plastic repair. Some of these, together with their clinical results, will now be surveyed. Besides the patients needing repair of postoperative or ventral hernia, patients with recurrent inguinal hernia, knee joints with excessive lateral motion, rupture of the biceps tendon, conditions of the finger tendons requiring plastic operations and other conditions (table 2) have been treated with the cutis transplant.

The repair of recurrent inguinal hernia by this procedure was done in 11 cases. Three patients showed recurrence of the hernia after the cutis repair, but the others have remained cured to date, the periods ranging from two to six years. Frank [8] in a recent paper reviewed these cases. From the sketches made at the operation, he found that in the repair of such a hernia a sufficiently large graft must be taken to assure good attachment to the surrounding structures. These attachments are primarily to the symphysis pubis below and to the internal abdominal muscles above, since recurrences usually develop at these points.

The plastic repair of a knee joint with excessive lateral motion by a cutis transplant has been an interesting step in the treatment of this disabling ailment. The cutis graft in such a case is a functional equivalent of the weakened ligamentous supports and aids in checking the lateral motion. Prior to 1933 Rehn made an S-shaped incision along the lateral or medial aspect of the knee, depending on the side on which weakness was present. With the knee slightly flexed, he exposed the lateral or medial muscle groups above the knee and the ligaments around the knee joint. Then he fastened the upper pole of the cutis graft to these. The lower pole he sewed under tension to the previously exposed tuberosity of the tibia below. At present, however, he makes one incision above and one below the knee joint, as illustrated in figure 7.

After freeing the adipose tissue from the outer ligamentous structures of the knee by means of blunt dissection, he sews the cutis to the muscles exposed by the upper incision. Through the incision below the knee he then inserts forceps, drawing the cutis flap down and fixing it under tension to the gastrocnemius muscle. Fixation sutures are then placed at all available points to assure firm attachment of the graft. Rehn no longer attaches the cutis to the tuberosity of the tibia, since the muscular attachment affords more equalized tension than the bony one. In 1 case reported by Brandis [9] the excess lateral motion was marked in both directions, and a bilateral plastic repair was performed, which has given an excellent functional result to date. The patient can again

8. Frank, R.: Grenzen der Bassini Operation und Indikationen zur Kutis Plastik, to be published.

9. von Brandis, H. J.: Zentralbl. f. Chir. **60**:130, 1933.

pursue all sports without hindrance. Eight patients with excessive lateral motion of the knee joint have been operated on in the clinic in this manner, with good results in 6 instances. Of the remaining 2 patients, 1 had a slight patellar snap on full extension of the knee but not lateral motion on extension; the condition of the other has remained unimproved. In the cases in which no improvement occurred, it was found that the muscles were not able to maintain the tension under which the cutis was attached, since they had become weakened by the long-standing condition which had allowed lateral motion. When this condition exists, the possibilities of a good result are slight. In all these cases some degree of lateral movement could be induced when the knee was flexed but not when it was extended. Results in the other cases in which operation and repair with the cutis technic were performed are given in table 2.

Fig. 7.—Sketch of the approximate position of the cutis graft with relation to the muscle groups and surrounding structures in the repair of knee joints with excessive lateral motion.

Two of these cases are of particular interest. In the first, a cutis transplant was used in the operative treatment of habitual dislocation of the jaw, and in the second the graft was used in conjunction with an arthroplasty which was performed because of an ankylosed elbow joint (fig. 8). The latter case was reported by Rehn.[10] The arthroplasty gave a good result without any limitation of motion until three years after operation, when the patient fell and fractured an epicondyle. Since that time the patient has been unable to extend the forearm fully. The other patient has had no recurrence of the dislocation.

Associated with any operative procedure are complications which may arise unexpectedly. Complications do occur after cutis plastic operations, but the majority of them do not necessarily cause a poor result.

10. Rehn, E.: Zentralbl. f. Chir. **61**:1563, 1934.

Good anesthesia contributes to a good result. The anesthesia must be sufficiently deep to assure complete relaxation of the muscles, so that the necessary degree of tension is sustained. Without sufficient relaxation, the cutis, which appeared tense at operation, will later relax and recurrence will be imminent. Spinal anesthesia and intravenous anesthesia have been tried, but ether anesthesia has given the best results.

Wound infection and hematoma formation comprise the principal early complications but are not so serious as one might expect. Fifteen of 104 patients had wound infections, and 5 had hematomas, complicating the postoperative course (table 3). In 9 of the first group,

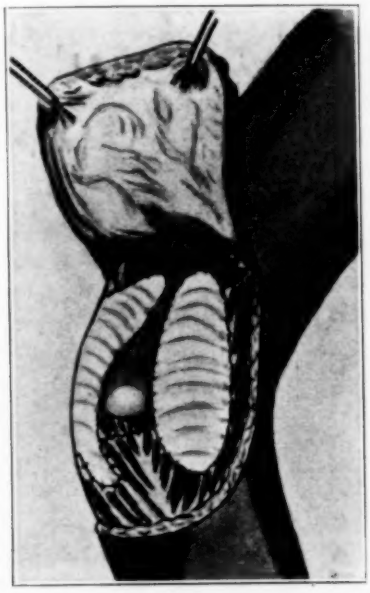

Fig. 8.—Half-schematic representation of the cutis graft in an elbow arthroplasty, as the functional equivalent of the ligaments.

there was good healing in spite of the infection, and no recurrence of the preoperative symptoms was observed. Two patients failed to appear for examination. Of the remaining 4 patients, 3 had erysipelas of the wound and the fourth a streptococcic infection. Neither of these was benefited by the operation. A severe wound infection caused by virulent aerobic or anaerobic organisms precludes a good result. Nonspecific infections cause little uneasiness, since the graft is active and metaplasia will proceed despite the infective process. Of those patients in whom a hematoma developed (the hematomas were usually caused by insufficient hemostasis of the bed of the wound), all but 1 had a normal postoperative course after the aspiration of the hematoma.

These figures show conclusively that complications by infection tended to hinder in only a slight degree the regenerative potentialities of the transplant and that antipathy to skin as a potential source of infection is probably unfounded. Fat necrosis with secretion, which often accompanies the simple infective process, requires local compress treatment for a few days, after which the wound heals per primam intentionem. The area of the thigh from which the cutis was taken healed somewhat slowly, but in all cases after six months' time the scar was scarcely visible.

The question of length of hospitalization or of the influence of the age of the patient on recovery may arise. All patients were kept in bed from four to ten weeks to assure good healing. Of all the cases, including cases of both ward and private patients, the average duration of hospitalization was from six to ten weeks for the former and from four to six weeks for the latter. The average age of all the patients was 51 years. The youngest patient was 5 years old, and the oldest was 85.

TABLE 3.—*Complications Following Plastic Operations with Cutis*

Complications	Number	Good Results	Poor Results	Results Unknown
Wound infection	15	9	4	2
Hematoma	5	4	1	..
Death from pneumonia	4	..	..	..

Both of these showed good postoperative results four years after operation. This would indicate that the patient's age has no important influence on the result of plastic operation with cutis.

SUMMARY

In this article a type of plastic operation performed at the clinic of Prof. E. Rehn in Freiburg, Germany, is described. The cases of the 104 patients operated on by this procedure since 1928 have been analyzed in the hope that the recorded results may stimulate the further use of the cutis transplant. Cutis is better suited for plastic repair than fascia, for it is active and has a longer life than the latter. Cutis is more easily available, since the graft can be taken from any area of the body; the source of fascia, on the other hand, is limited. In adipose persons, fascia is generally friable and thin and can be excised only in strips, but with cutis no such limitations exist. The removal of fascia incurs the risk of a postoperative muscle hernia. No herniation of the area from which the cutis was excised occurred in the cases just reviewed. Furthermore, cutis encourages tissue regeneration by the functional stimulus evoked by the tension under which the graft had been sewn. Generally metaplasia progresses despite wound infection. The operative procedure is not

difficult. If the operative areas are carefully prepared, a good anesthetic administered and the cutis graft sewn to the base of the wound as described, the patients will in the majority of instances show excellent postoperative results.

CONCLUSIONS

In any plastic operation in which cutis is used the following essential principles must be observed:

1. The skin in the operative area must be given careful preoperative preparation.

2. All necessary corrective procedures must first be attended to, such as the Bassini repair of an inguinal hernia or a Mayo-Pfannenstiel reconstruction of an abdominal hernia, before the cutis graft is sewn in place.

3. The muscle and fascia groups to which the cutis is to be attached should be anatomically dissected out and brought into view to facilitate good fixation of the graft.

4. All bleeding vessels in the wound bed must be ligated prior to transplantation to prevent formation of a postoperative hematoma.

5. It is all important that the cutis graft be sewn to the surrounding tissues under the greatest possible tension.

MESENTERIC LYMPHADENITIS

REPORT OF TWENTY-FOUR CASES WITH TABULATIONS SHOWING RELATION TO APPENDICITIS AND OTHER DISEASES; NEED OF BETTER UNDERSTANDING OF THE MESENTERIC LYMPH NODES

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A continuation of the review of the hospital charts from Aug. 1, 1936 to Sept. 1, 1937 on which has been noted a definite record of diseases of the mesenteric lymph nodes shows more than was reported in the detailed analysis covering 123 cases observed during the years from 1914 to Aug. 1, 1936, previously published.[1] Proportionately, as has been pointed out, more attention is being paid to the lymphatic system generally and particularly to the lymph nodes within the abdomen than was given to these structures ten or twenty years ago. It was much longer ago than this, however, that tuberculosis was believed to be the cause of most lesions of the mesenteric nodes; attention was given to nonspecific mesenteric lymphadenitis only about 1920 and thereafter.

Numerous articles have appeared since 1900 reporting the association of the symptoms of mesenteric lymphadenitis with those of infection in the vermiform appendix. Some authors have said that mesenteric lymphadenitis is indistinguishable from certain types of appendical disease, and others have gone so far as to say that mesenteric lymphadenitis can be readily differentiated from appendicitis before operation or even without operation. I hesitate to agree with the latter.

It is high time that a more definite understanding be reached between practicing physicians and investigators of the disease syndrome called mesenteric lymphadenitis. From the observation of 123 case histories previously studied and of 24 additional cases for comparison, I believe that certain definite statements on the various characteristics of the disease can be given out.

For detailed development of the hypothesis that stasis in the gastrointestinal tract, chronic disease of the liver, constipation and many other conditions may predispose to the development of infection of the mesenteric lymph nodes the original article must be referred to.[1] That

From the New York Post-Graduate Medical School and Hospital, Columbia University.

1. Foster, A. K., Jr.: Disease of the Mesenteric Lymph Nodes: Its Relation to Appendicitis, Infections of the Gastro-Intestinal Tract, and Generalized Diseases; Report of One Hundred and Twenty-Three Cases; Discussion of Possible Etiology and Treatment, Arch. Surg. **36**:28-52 (Jan.) 1938.

appendicitis of different types may be associated with involvement of the mesenteric nodes is indicated by the observations in the 123 cases previously reported and also by the profuse literature on the subject, which is probably not sufficiently appreciated.

It cannot be denied that there is a discrepancy between the clinical descriptions of mesenteric lymphadenitis given by some investigators and the findings of the majority of surgeons operating in the abdomen. The reason for this is that many have neglected to notice the condition of the mesenteric lymph nodes at the time of operation. There is a great difference in clinical opinion as to the normal limits in size of the lymph nodes and the anatomic characteristics of disease in the deeply buried lymphatic structures of the mesentery. Careful thinking on the subject, however, does not permit an escape from certain definite opinions on the questions of diagnosis and treatment.

Further proof than that a patient with infection of the cervical lymph nodes had an original portal of entry of the offending germ somewhere in the mouth or the upper part of the respiratory tract is seldom given any serious consideration unless the point of entrance is still causing trouble or is believed to be continuing the pathologic process in the lymph nodes of the neck. Infected teeth, tonsils and sinuses are all old subjects now, a little out of style and somewhat hackneyed as a topic for discussion. In spite of this the surgeon must maintain an interest in the cause of infection of the glands of the neck, and he does this by insisting on good cooperation from the otolaryngologist. The surgeon, then, recommends that the teeth and upper respiratory tracts of all patients be studied for the point of origin of the infection. Often there is little to account for the cervical infection, which is seldom diagnosed from a truly scientific point of view.

So it is with the operative finding of infection of the mesenteric lymph nodes. As a rule the operator takes out a mildly diseased appendix, hoping that a diagnosis of chronic appendicitis will satisfy the patient and that appendectomy will produce good results. The feeling that there is some other cause than "just a chronic appendix" has stimulated discussion as to what does cause the atypical abdominal symptoms which sometimes occur and are not relieved by a simple appendectomy. No one seems to have answered this question conclusively.

It is only natural that the majority of practitioners must become confused by such a state of affairs. The opinion of the most careful of clinical investigators on the subject of intra-abdominal disease should be emphasized more frequently than it is: namely that every case should be studied individually, so as not to receive a much abused general diagnosis or one based on few physical signs and no truly scientific principles.

There is good evidence that chronic appendicitis should be discarded as a blanket diagnosis covering all the indefinite pathologic conditions which frequently lead to celiotomy. There is good evidence, furthermore, that the mesenteric lymph nodes and the large plexus of lymphatics in the mesentery have been underestimated, to say the least, as to their function and import in physical diagnosis.

If the analogy of infection of the cervical lymph nodes may again be alluded to, it would be wise to remember that tonsillitis with its attendant involvement of the lymph nodes is seldom given the additional diagnosis of cervical lymphadenitis. So, likewise, at the time of celiotomy, few surgeons have bothered to note the presence of mesenteric lymphatic infection until comparatively recently, unless no other diagnosis for the intra-abdominal symptom could be reached. None the less, however, they probably have been persistently correct in removing the appendix, for of course numerous patients have remained well and have never been seen again. If little emphasis was ever put by these surgeons on the mesenteric lymph nodes, there can be little hope of proving that the nodes were ever involved, providing the patients have generally remained as well as they have appeared to do.

On the basis that infection in the mesenteric lymph nodes is comparatively common but is insufficiently appreciated as being able to give rise to symptoms either alone or in conjunction with many other conditions, I should like to emphasize to all physicians who diagnose intra-abdominal disease that infection of the mesenteric lymph nodes is a real entity and is not to be forgotten at any time.

When it is diagnosed or suspected it cannot be safely dropped from consideration, or "shelved." It should mean that the physician has accounted for some of the symptoms. In addition, his discovery that the lymph nodes are affected should indicate to him that an extensive and important group of structures must be included in his consideration of the possible cause of the condition, the treatment and the prognosis. A great step will have been taken when surgeons have learned that the mesenteric lymph nodes are as important in relation to the rest of the gastrointestinal tract and to the appendix as are the cervical nodes to the upper respiratory tract and, for example, the teeth. One must not forget, moreover, the importance of the remainder of the lymphatic structures in the body, especially the largest groups of all, the mesenteric and retroperitoneal groups.

Any proof that the surface lymph nodes of the body are all involved in any pathologic changes, either acute or chronic, should point to the likelihood, if not the certainty, of similar changes in the intra-abdominal lymph nodes. A moment's recollection of the close anatomic connection between the branches of the splanchnic nerves, the

nerve plexuses, the branches of the mesenteric vessels and the mesenteric lymph nodes—which are contiguous—must be of value to the physician who wishes to arrive at any conclusion about vague disease symptoms in the abdomen. The innumerable pathways of the mesenteric plexus and the symptoms that might arise from the countless irritations of the vasomotor nerves in the walls of the mesenteric vessels which may have been stimulated by infection of the mesenteric lymph nodes offer endless considerations as to refinement of diagnosis, but unfortunately little that is uniform and consistent enough to teach as a real symptom complex.

Because of the fact that some investigators have been very definite about the ease with which mesenteric lymphadenitis can be diagnosed, I feel that this teaching should be discontinued. My statement that the condition is not always easy to diagnose is given weight by the numerous authors who have frankly admitted the difficulty of ruling out atypical appendicitis and have been mentioned earlier.[1]

The frank interpretation of cases studied at the New York Post-Graduate Hospital over a long period of years seems to bear out this statement.[1]

From the first study and also from the cases observed from Aug. 1, 1936 to Sept. 1, 1937 in the same hospital, it is apparent that when the mesenteric lymph nodes are noted at operation to be diseased, there may have been many and varied symptoms; the condition may have been acute, or it may have been subacute or chronic, with abdominal distress dating back many years. There are cases of intra-abdominal malignant neoplasm with infection in the mesenteric nodes that could not possibly be diagnosed preoperatively by any of the syndromes which have been attributed to either acute or chronic mesenteric lymphadenitis.

Each patient must receive a careful physical examination, including especially a search for foci of infection in the upper part of the respiratory tract, the gallbladder, the colon, the rectum and the appendix. Ova and parasites must be ruled out. Stasis in the gastrointestinal tract, recurrent abdominal symptoms of even mild digestive distress, spasm of the rectal sphincter and constipation must all be recorded if the cause of the disease of the lymph nodes is to be understood and properly treated.

In the cases of mesenteric lymphadenitis it is most important to note that there may be no abdominal signs whatever, or there may be only a tenderness to the right of the umbilicus at McBurney's point or a little above it. Spasm and rigidity are less common, and when they occur they do not help much either to rule out the diagnosis or to establish it. Some physicians apparently do not note the special signs, such as the shifting dulness when the patient turns on either side, or the shift in the tender-

ness to the left of the umbilicus when he turns on the left side. Such physical signs as either of these are open to considerable misinterpretation, although they should not be forgotten.

The diagnosis is not regularly made preoperatively, nor is the condition found alone except in extremely rare cases. In this hospital the positive proof of an infection in the appendix at some time has been found in almost 90 per cent of all operative cases of mesenteric adenitis.

The treatment is most important and requires particular emphasis. The patients for whom nothing but simple appendectomy was performed showed an entirely different mortality and morbidity average from that observed among patients on whom a more extensive operation was performed. The comparison, of course, is similar to a comparison of a number of different diseases, any and each one of which may carry its own higher rate in complete independence of the "incidental" mesenteric lymphadenitis. The low rate of occurrence of complications of all kinds when simple appendectomy was done would indicate that the time has come to encourage the removal of the appendix, not only because there is nothing else to remove but also because of this little appreciated disease, mesenteric lymphadenitis. It especially should be described to the patient and cited as a reason that something is wrong besides "just an appendix." A complete search for the underlying causes of the disease ought also to be made.

I believe the patients with insufficiently studied mesenteric lymphadenitis, for whom a vague diagnosis is made and who are not given a new hygienic regimen so as to do away with their deep-seated predisposition to infection of the mesenteric lymph nodes (if it is not entirely due to infection or malposition of the appendix) compose the large group who are not relieved by appendectomy and often require a later celiotomy.

I feel that certain organs are sites of predilection for certain organisms and that when a lymph node shows involvement it must indicate that the infection has already gone by some barrier to reach the node. It must mean that the infection is one that elects to infect lymph nodes or one by which the lymph nodes are especially affected. Further, it must mean that when several nodes are affected there is a strong likelihood that extension to the next group of lymphatics or to the blood stream itself (as in peripheral adenitis and lymphangitis in an extremity) may occur when the mesenteric infection is not well understood and treated. The work of Braithwaite [2] admirably bears out this belief. Heyd [2] has done much to point out many of the steps taken by disease in the abdomen to affect the liver—often by way of the lymphatics. He

2. Cited by Foster.[1]

is in complete agreement with Alvarez and Adami on the subject of subinfection of the gastrointestinal tract as a cause of hepatic disease and of repeated insults to the mesenteric lymphatics.

TABLE 1.—*Age and Sex Incidence*

Age	Number of Cases	Male	Female
Under 1 year	0	0	0
1- 6 (incl. 6)	5	3	2
7-10 (incl. 10)	5	3	2
11-16 (incl. 16)	2	1	1
17-21 (incl. 21)	4	0	4
22-29 (incl. 29)	3	1	2
30-37 (incl. 37)	0	0	0
38-72 (incl. 72)	5	2	3
Total	24	10	14
Under 21	16	7	9
21 and over	8	3	5
16 and under	12	7	5
10 and under	10	6	4

TABLE 2.—*Data in Twenty-Four Cases of Mesenteric Lymphadenitis*

Average age	19.4 yr.
Sex	10 M, 14 F
Died	1, or 4%
Acute appendicitis	2, or 8%
Subacute appendicitis	11, or 46%
Chronic appendicitis	9, or 38%
Appendectomy	21, or 88%
Other operations	9, or 38%
Evidence of upper respiratory tract or marked focal infection	6, or 25%
Evidence of disease in appendix at any time	21, or 88%
Clinical mesenteric tuberculosis	3, or 13%

TABLE 3.—*Further Data in Twenty-Four Cases of Mesenteric Lymphadenitis*

Average age	19.4 yr.
Sex	10 M, 14 F
Chronic mesenteric lymphadenitis	20, or 84%
Acute mesenteric lymphadenitis	3, or 12%
Purulent mesenteric lymphadenitis	0 0
Pronounced clinical mesenteric tuberculosis	3, or 12%
Associated appendical disease at any time	21, or 89%
Associated visceroptosis or constipation	8, or 34%
Fecal material+ or fecalith++ in appendix	11+, or 44% 5++, or 21% 16, or 68%
Associated gallbladder disease at any time (proved)	2, or 8%

It will be interesting to note a few brief summary tables of the findings in cases of mesenteric lymphadenitis observed at the New York Post-Graduate Medical School and Hospital from Aug. 1, 1936 to Sept. 1, 1937, so as to compare them with what was previously found.[1]

The most interesting findings in these tables have to do with what has gone before. The study of the first 123 cases of mesenteric lymphadenitis recorded in this hospital during a period of twenty-two years revealed certain apparent results.[1] There was a chance to check them because the first half of the group were tabulated separately and at different times before data on the second half were added to the statistics.

The fact that as many as 24 additional cases were observed in the year following the recording of the first large series makes the close inspection of these 24 case records especially worth while. This is true particularly because of the almost identical percentages and averages in this small series and in the original, larger groups.[1]

TABLE 4.—*Summary of Clinical Findings*

Average age	19.4 yr.
Sex	10 M, 14 F
Preoperative vomiting	12, or 50%
Distention or tympany	2, or 8%
Spasm of abdominal muscles	4, or 16%
Abdominal mass	2, or 8%
Rigidity	2, or 8%
Tenderness	13, or 54%
Recurrent preoperative symptoms	20, or 84%
Average white blood cell count	9,500
High average preoperative temperature	100.2 F.
High average preoperative pulse rate	90
High average postoperative temperature	101.9 F.
High average postoperative pulse rate	115
Other abdominal disease	11, or 46%
Clinical tuberculosis of the mesenteric lymph nodes	3, or 12%
Deaths	1, or 4%

CONCLUSIONS

Mesenteric lymphadenitis is a little understood disease that cannot always be diagnosed alone but must not be considered any the less important because of this fact.

Vague abdominal symptoms not apparently caused by any definite disease of any particular organ should draw the physician's attention to the mesenteric lymph nodes, if only because of the intimate association between the mesenteric nerve plexus, the mesenteric arteries and veins and the mesenteric lymph nodes themselves.

The high incidence of stasis in the gastrointestinal tract both in this series of cases and in the cases of the earlier report [1] seems to offer the best approach to the problem of determining the most healthful regimen for the patient on whom appendectomy is performed for this disease.

The mesenteric lymphatics are not sufficiently emphasized as to their functional importance both in health and in disease. The average layman

knows about the "glands" in the neck, but he and many physicians know little or nothing of the function of the largest group of lymph nodes and lymphatics in the body—the mesenteric and retroperitoneal groups. Medical and lay teaching should include more detailed studies of these structures.

Appendectomy is the treatment for mesenteric lymphadenitis; it should be performed as soon as the diagnosis is made. Indications of other intra-abdominal disease do not furnish any excuse for neglecting the appendix. Other pathologic conditions of the abdomen should likewise indicate the need of surgical intervention in addition to appendectomy, when necessary.

Infection involving lymph nodes in any part of the body (especially in the neck) should remind the examiner of the numbers of mesenteric nodes which may be also infected.

The vermiform appendix becomes more important than ever before because of the high percentage of diseased appendixes observed in a total series of 147 cases of mesenteric lymphadenitis (in all but 2 of which the diagnosis was proved), from the records of the New York Post-Graduate Medical School and Hospital, Columbia University. The last 24 of these cases are tabulated in this paper, and the data closely resemble those in the cases already reported.[1]

SPLENECTOMY IN TREATMENT OF PROVED SUBACUTE BACTERIAL ENDOCARDITIS

REPORT OF A CASE AND REVIEW OF THE LITERATURE

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A case of proved subacute bacterial endocarditis in which the condition was treated by splenectomy is herewith reported in detail. The patient is alive and well at the time of writing, more than twenty months after splenectomy. I recognize that twenty months is a short time, but the patient is so completely well that when one considers how hopeless the outlook was only a few months before, the case seems worth reporting.

REVIEW OF LITERATURE

In reviewing the literature I discovered that the effort to alter by splenectomy the insidious course of subacute bacterial endocarditis had been made first in the United States by Riesman,[1] then in Europe by Nordmann,[2] then in South America by Escudero and Merlo [3] and finally in Russia by Sawadski.[4] Other sporadic efforts have been reported by the Mayo Clinic,[5] by Heilborn,[6] by Wieden [7] and by Riesman, Kolmer, and Polowe.[8]

A critical analysis of the 15 csaes thus reported shows that in only 3 was the diagnosis proved prior to operation by cultures of the blood.

From the Nathan and Miriam Barnert Memorial Hospital.

1. Riesman, D.: Chronic Septic Endocarditis with Splenomegaly: Treatment by Splenectomy, J. A. M. A. **71**:10 (July 6) 1918.

2. Nordmann, A., in discussion on Endocarditis lenta, Verhandl. d. deutsch. Gesellsch. f. Chir. **45**:240, 1921.

3. Escudero, P., and Merlo, E. V.: Splenectomy in the Treatment of Endocarditis, Rev. de la Soc. de med. int. **1**:361, 1925.

4. Sawadski: Russk. klin. **4**:875, 1925.

5. Mayo, W. J.: Surgical Aspects of Diseases of the Lymphoid Organs, with Special Reference to the Spleen, in Collected Papers of the Mayo Clinic and the Mayo Foundation, Philadelphia, W. B. Saunders Company, 1929, vol. 21, p. 638.

6. Heilborn, E.: Is It Possible to Influence Ulcerative Endocarditis or Sepsis by Extirpation of the Spleen? Med. Klin. **22**:535, 1926.

7. Wieden, L.: Splenectomy and Re-Examination of Persons Subjected to It: Twenty-Year Follow-Up, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **44**:13, 1935.

8. Riesman, D.; Kolmer, J. A., and Polowe, D.: Splenectomy in the Treatment of Subacute Bacterial Endocarditis, Am. J. M. Sc. **192**:475, 1936.

The patients in all 3 of these cases were dead within fifteen weeks after splenectomy. One died four weeks after the operation, of femoral and pulmonary embolism; 1 died eight weeks after the operation, of cerebral embolism; 1 died fifteen weeks after the operation, also of cerebral embolism.

It appears, then, that the case herein reported is the first proved case of subacute bacterial endocarditis in which the patient recovered after splenectomy.

Of the 12 patients in whose cases the diagnosis was not proved, 6 were dead within three months after splenectomy, 4 died between seven and twelve months after splenectomy and 2 were alive and well at the time the reports were made (1 six months after splenectomy; the other when he left the hospital). Both the proved and the unproved series are too small to be useful in the drawing of safe conclusions. Thus far, one may state with caution that splenectomy may prove to be most beneficial in cases in which subacute bacterial endocarditis is suspected but is unproved. A summary of opinions of the benefits to be derived from splenectomy in the treatment of subacute bacterial endocarditis may be helpful.

1. In a general article on the spleen, W. J. Mayo [5] in 1929, in discussing various types of septic splenomegaly, stated that splenectomy done for the relief of subacute bacterial endocarditis was without benefit to his patients. Giffin [9] has given me data on 2 of Mayo's cases in which splenectomy was done and in which the patients were probably suffering from subacute bacterial endocarditis. Both of these patients died at home, one three months and one seven months after splenectomy; permission for necropsy was not obtained. A single culture of the blood in each case was sterile. The diagnosis was made from the clinical symptoms. Pathologic examination of the spleens showed nothing of diagnostic importance; there was considerable decrease in fibrous tissue.

2. Nordmann [2] stated that a patient with endocarditis lenta was splenectomized by him four months previous to the time of his report and was doing well. A second patient had been operated on a few days previously and also was doing well. (See follow-up on these two cases by Heilborn.) Nordmann stated that his rationale is that splenectomy serves as a stimulus to the remaining endothelial system in the liver, the bone marrow and the lymph glands, thus stimulating erythropoiesis and leukocytosis.

3. Heilborn [6] reported the end results in Nordmann's 2 cases. The patient in the first case returned to work eight weeks after splenectomy, feeling entirely well. Six months after splenectomy he died of cerebral embolus. Prior to splenectomy this patient had all the symptoms of

9. Giffin, H. Z.: Personal communication to the author.

endocarditis lenta. Five days before admission he had noticed a sudden, severe pain in the left side of the hypochondrium. When removed the spleen exhibited several recent infarcts. It was enlarged, but no bacteria were found.

The second patient had complained of dyspnea and sweats associated with elevation of temperature in the evening. The diagnosis was endocarditis. Several cultures of the blood were sterile. This patient improved after the removal of a large splenic tumor. Cultures of the blood made postoperatively showed a few colonies of diplococci. Three weeks after operation the patient became much worse. Symptoms of aneurysm developed, and a few months later he died of a ruptured aneurysm with terrific hemoptysis. This patient had had syphilis a few years before; he had been heavily treated with antisyphilitic therapy, and his Wassermann reaction on admission to the hospital was negative.

Heilborn concluded that the improvement following splenectomy in cases of endocarditis lenta can be explained only through the elimination of one of the chief foci of infection. He stated that splenectomy performed early in the course of the disease should give good results. One of the indications for splenectomy in this condition is severe pain in the splenic area.

4. Escudero and Merlo [3] reported a proved case of subacute bacterial endocarditis; there was a history of syphilis. While the hypochondriac pains disappeared after splenectomy, the general condition remained unchanged. The patient died a month or so later of pulmonary embolism. The spleen was enlarged; it contained multiple infarcts and exhibited slight perisplenitis. These authors expressed the opinion that splenectomy was not justifiable in this condition.

5. Sawadski [4] reported a case of subacute bacterial endocarditis in which the condition was treated by splenectomy. The patient was alive and well at the time of the report, six months later. The diagnosis was not proved, but Sawadski stated that bacteremia is not a contraindication to splenectomy. He concluded that the spleen in this condition acts as a focus of infection.

6. Wieden [7] reported 5 cases. In 1 case, in which the patient did well but could not be traced, the diagnosis of endocarditis was doubtful. In no instance were cultures of the blood reported, if they were done. In 3 cases the diagnoses were obtained at postmortem examination, one diagnosis being endocarditis lenta, the second being lymphatic leukemia and endocarditis and the third being recurrent vegetative endocarditis. In a fifth case, in which the patient died two months after the splenectomy the diagnosis could not be confirmed, as no autopsy was done. In spite of the poor results obtained, Wieden felt that splenectomy is justified because with the spleen is removed, in some cases, the main focus of infection.

7. Riesman, Kolmer, and Polowe,[8] in summarizing their conclusions based on 4 cases plus a review of the 11 cases previously mentioned, stated:

> Splenectomy may prove to be a method of dealing with intractable forms of sepsis without discoverable focus in which splenomegaly is a prominent feature. This group, in which subacute bacterial endocarditis may be suspected but is unproved, at present promises the best results from the operation.

8. My own opinion is based on 2 proved cases, case 2 reported in the tripartite paper aforementioned [8] and the case herein reported. I believe that when subacute bacterial endocarditis manifests progressive secondary anemia associated with splenomegaly and pain in the left side of the hypochondrium, splenectomy is of definite palliative value. Such splenectomy seems to act as a substitute for transfusions by arresting the progress of the anemia and producing ultimate improvement in the hemoglobin and erythrocyte content of the blood. The white blood cell content is increased, and in cases in which the condition is associated with thrombocytopenia the platelet count is lifted to normal levels. Abdominal and articular pains have disappeared after splenectomy, and a quieting effect on the action of the heart has been noted. I believe that the spleen is a continuous source of reinfection and of absorption of bacterial toxins. In both cases the patients' chief complaint, abdominal pain, was entirely relieved. The first patient died fifteen weeks later of cerebral embolus. The second patient is alive and well more than twenty months later. A detailed report of the successful case follows.

REPORT OF CASE

A white girl aged 12 complained of weakness, anorexia and pain in the left upper quadrant of the abdomen, of two months' duration. The family history was noncontributory. The patient's tonsils and adenoids had been removed in 1930. She had had an attack of acute pyelitis in 1931. Her health had been otherwise satisfactory.

About the middle of March 1937 the patient was taken to one of the hospital clinics. No diagnosis was made, but she was ordered to report back to the clinic for patients with cardiac disease. The parents then put the patient to bed, and I was called in to see her on the night of March 17.

Physical Examination.—The temperature was 105 F. and the pulse rate 90; the pulse was regular. The respiratory rate was 20, and the respirations were normal. The blood pressure was 108 mm. of mercury systolic, and 64 mm. diastolic. The weight was 69 pounds (31.4 Kg.). There was some evidence of wasting, and the patient had a pale, wan look.

The lower molars on both sides were decayed. The tongue was coated. There was one petechial hemorrhage in each conjunctival sac.

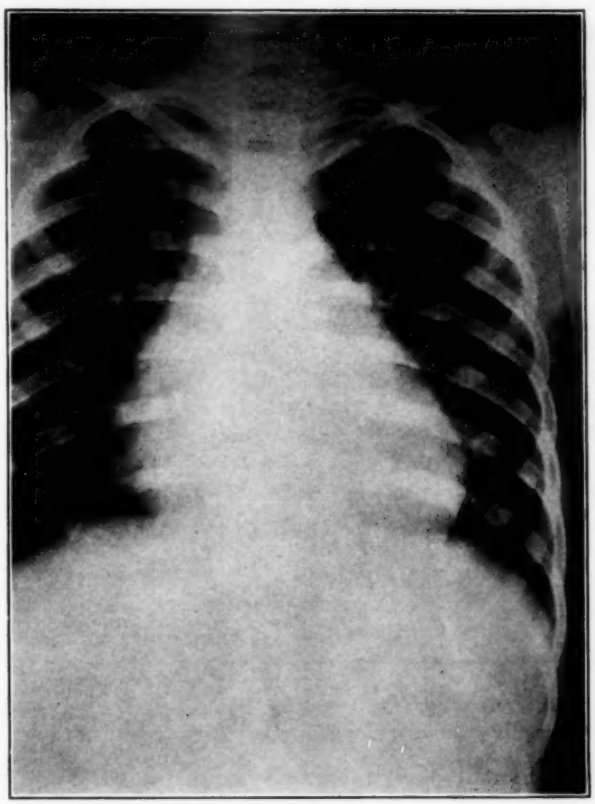
The glands in the cervical, axillary and inguinal regions were easily palpable.

The lungs were normal. The heart disclosed a mitral systolic murmur, which was transmitted a short distance into the axilla. The heart was enlarged, the point of maximal impulse being almost at the nipple line (see illustration).

The abdomen was soft. Tenderness over the splenic area was easily elicited. The spleen was enlarged so that the lower pole of it rolled over the examining fingers. The liver was enlarged downward almost to the level of the umbilicus.

Vaginal and rectal examinations were not done, except to inspect the introitus for the possible presence of vaginitis. There was no evidence of vaginal discharge; the mucosa looked clean and healthy.

There was one ecchymotic area on each tibial surface in the upper third of its length.



Roentgenogram of the chest. There is no evidence of pulmonary infiltration. The cardiac shadow is enlarged, with obliteration of the pulmonic curve, which is indicative of a lesion of the mitral valve.

The deep and superficial reflexes were intact.

Laboratory Findings.—The results of examination of the blood are presented in table 2.

A culture of the blood was made March 18. The report, one week later, was "no growth." A second culture was made April 7. The report, several weeks after splenectomy, was "pure culture of streptococci obtained in anaerobic medium." This could not be further identified on the ordinary subculturing mediums. It should be noted that splenectomy was performed before positive knowledge of the underlying disease was obtained.

Biopsy of material from the right axillary lymph gland, removed March 25, was reported on by Dr. Hans Wassing, pathologist, as follows: "Nonspecific hyperplastic and chronic inflammatory (?) changes."

TABLE 1.—*Summaries of Proved and Unproved Cases of Subacute Bacterial Endocarditis in Which Splenectomy Was Done*

No.	Date Reported	Where Done	Age	Bacteria in Cultures of Blood?	Final Results and Comment
		Group 1: Proved Cases in Which Splenectomy Was Done			
1	1925	Argentina.....	28	Yes	Dead 4 weeks after operation; pulmonary and femoral embolism
2	1936	Paterson, N. J.....	25	Yes	Dead 15 weeks after operation; cerebral embolism
3	1936	Philadelphia.....	22	Yes	Dead 8 weeks after operation; cerebral embolism
4	1938	Paterson, N. J.....	12	Yes	Alive and well more than 20 months after operation; see text of this paper for details
		Group 2: Unproved Cases in Which Splenectomy Was Done			
1	1918	Philadelphia.....	57	No	Improved strikingly, then died 4 weeks after operation of abscess of larynx
2	1921	Berlin, Germany.....	31	No	Alive and well for 6 months, then died of cerebral embolism
3	1921	Berlin, Germany.....	27	No	Dead 3 weeks after operation; ruptured aneurysm
4	1925	Russia.....	28	No	Alive and well at time of report, 6 months later
5	1929	Rochester, Minn.....	10	No	Dead 3 months after operation; cause unknown
6	1929	Rochester, Minn.....	37	No	Dead 7 months after operation; cause unknown
7	1935	Prague, Czechoslovakia.	21	No	Alive and well at time of report; diagnosis doubtful
8	1935	Prague, Czechoslovakia.	40	No	Dead 2 months after operation; cause unknown
9	1935	Prague, Czechoslovakia.	24	No	Dead 3 months after operation; cause unknown
10	1935	Prague, Czechoslovakia.	57	No	Dead 1 year after operation; lymphatic leukemia
11	1935	Prague, Czechoslovakia.	27	No	Dead 3 weeks after operation; cerebral embolus
12	1936	Philadelphia.....	30	No	Improved, then died 7 months after operation; cause unknown

TABLE 2.—*Preoperative and Postoperative Blood Picture in Proved Case 4*

Date, 1937	Hemoglobin, Percentage	Red Blood Cells, Millions	White Blood Cells, Thousands	Polymorphonuclears, %	Lymphocytes, %	Mononuclears, %	Coagulation Time in Minutes	Bleeding Time in Minutes	Clot Retraction	Platelets
3/18	63	3.8	7.1	62	30	8				
3/22	64	3.8	6.5	68	28	4	...	.....	.....	40,000
3/24	..	4.1	5.9	53	43	3	5.5	Over 15	None	32,000
4/ 7	63	3.4	3.6	82	17	1	3.5	Over 15	None	18,000
4/ 9	..	...	4.6	55	44	1	...	.....	.....	35,000
4/10	Splenectomy performed									
4/12*	48	...	7.5	74	26	..	...	.....	.....	138,000
4/15	45	2.36	7.45	84	16	..	...	.....	None	186,000
4/20	43	2.24	...	72	28	..	...	.....	.....	160,000
7/10	85	4.32	11.0	50	44	4	...	.....	Prompt	240,000

* A slight Arneth-Schilling shift was found on 4/12/37. No shift was found on other dates.

The Widal test for typhoid and paratyphoid bacilli gave a negative reaction.

The agglutination test for undulant fever gave a negative reaction.

The Mantoux test (intradermal injection of 1:1,000 dilution of tuberculin) gave a positive reaction.

The snake venom test (intradermal) gave a positive reaction after one hour.

The Wassermann test of the blood gave a 4 plus reaction. The patient's father, mother and only sister (who was older) were tested in this laboratory and in two other laboratories. All reactions were negative. Specimens of the patient's blood serum were likewise sent to two other laboratories. Both laboratories reported a plus-minus Wassermann reaction. The state laboratory reported a 3 plus Kahn reaction. The laboratory of this hospital consistently reported a 4 plus Wassermann reaction. (See section on references to false positive Wassermann reactions in cases of subacute bacterial endocarditis.)

Repeated 4 plus benzidine reactions were obtained from chemical tests of the stool. Microscopically the stool contained no ova or parasites.

The urine repeatedly gave a 1 plus reaction to the test for albumin. It contained no sugar. There were fairly numerous red blood cells and numerous hyaline and granular casts.

Roentgenograms of the teeth, taken on March 23, gave no evidence of apical foci of infection.

Roentgenograms of the chest, taken on March 27, gave no evidence of tuberculosis. The cardiac shadow was enlarged, and obliteration of the pulmonary curve indicated a mitral lesion.

Preoperative Diagnoses.—After all the laboratory data were evaluated it was concluded that the patient was suffering from a generalized infection of unknown cause. [NOTE:—The second culture of the blood, made three days prior to splenectomy, was not reported as yielding bacteria until several weeks after the splenectomy.] However, the following conditions were considered the most important possibilities: (*a*) subacute bacterial endocarditis, (*b*) acute rheumatic cardiac disease and (*c*) congenital syphilis. Associated with the condition were caries of the teeth and a laboratory type of thrombopenic purpura haemorrhagica.

Preoperative Treatment.—During March and early April conservative treatment was followed; it included: (*a*) antisyphilitic treatment, because it had not yet been established that the strongly positive Wassermann reaction was false, (*b*) transfusions of whole blood, (*c*) injection of moccasin snake venom, and (*d*) administration of sulfanilamide, salicylates and liver extract by mouth.

The patient did not improve with these measures. She seemed worse. I recommended splenectomy to the family, because I felt that it would remove a source of toxicity, because of the extremely low platelet count, because it is known that syphilis (if this was a case of syphilis) when associated with splenomegaly responds better to antisyphilitic treatment following splenectomy (Mayo [5]), because of my conviction that splenectomy is beneficial in cases of subacute bacterial endocarditis, especially when the diagnosis is unproved (I again call attention to the fact that the splenectomy in this case was performed after the culture which yielded bacteria was done but before the report came in), and because I felt that splenectomy not only would be a substitute for transfusions but would be associated with some degree of leukocytosis (the reader's attention is invited to the persistent preoperative leukopenia which prevailed in this case). Several consultations were held with various physicians, and consent for splenectomy was finally obtained, though only one other physician agreed with me that splenectomy (aside from the operative risk) offered the patient some hope for recovery.

Operation.—Splenectomy was performed by me on April 10. The operation was well borne by the patient. It took one hour and four minutes. The patient made an uneventful operative recovery and was permitted to go home on April

19. A progress note as of April 18 reads: "The patient's appearance is wan; there is evidence of wasting. The eyes, however, look rested. The lymph nodes in the cervical, axillary and inguinal areas are smaller, and this adenitis seems to be subsiding. The heart is quieter. There is no abdominal pain."

The range of pulse rate, temperature and respiratory rate during the postoperative period of hospitalization was, respectively, 88 to 120, 100.4 to 104.6 F. and 20 to 32.

Gross Pathologic Change Found at Operation.—The spleen was enlarged to four times the normal size. There were many fine adhesions between the spleen, the overlying gastrointestinal structures, the liver and the diaphragm. The liver was enlarged, extending almost down to the umbilicus on the right side, while the left lobe was adherent to the overlying diaphragm by means of fine fibrous strands. The gallbladder was not visualized. There was no fluid in the abdomen.

Pathologist's Report (Dr. Hans Wassing).—Gross pathologic picture: The spleen was markedly enlarged and weighed 12 ounces (384 Gm.). There was definite evidence of perisplenitis (in patches). There were no infarcts. The consistency was medium. Microscopic pathologic picture: Slight increase in periarterial connective tissue was visible. The pulp was cellular. Polymorphonuclear leukocytes and plasma cells were somewhat increased. Levaditi stain of splenic tissue: Spirochaeta pallida were not found. Gram stain: Streptococci were not found. Material aspirated from spleen and cultured: No growth was obtained. Culture of material from the spleen: No growth was obtained.

Summary of Other Postoperative Laboratory Work.—The first postoperative culture of the blood was made on April 19, nine days after the operation. This was reported several weeks later as yielding anaerobic streptococci. These organisms were subcultured and grown under carbon dioxide tension by Miss A. Van Saun, bacteriologist-in-charge, Paterson Board of Health, City Laboratory. Miss Van Saun reported that the organism was Streptococcus viridans.

About three months after the operation another culture of the blood was made. This was reported several weeks later as having produced no growth.

On April 19, 1937, nine days after splenectomy, this laboratory reported the Wassermann reaction as plus-minus. This was repeated three months later, at which time the report came back as doubtful plus-minus.

The blood counts may be inspected at a glance in table 2. Attention is invited to the drop in the red blood cell count and in the hemoglobin immediately after splenectomy. Since there was no hemorrhage at operation or afterward, I attribute this drop to the loss of blood which normally circulates in the splenic sinuses. It should be noted that the patient gradually recovered this loss, so that three months after the operation the red blood cell count was over 4,000,000 and the hemoglobin content was 85 per cent.

Attention is also invited to the immediate rise in the white blood cell count and to the rise in the platelet count.

Postoperative Course.—The evening temperature range continued in levels between 103 and 104 F. until April 30. After that date there was a gradual decline to normal levels, which were reached on July 1. The temperature has remained normal since that date. The patient has gained in weight from 67 pounds (30.5 Kg.) to over 100 pounds (45.6 Kg.). She is back in school and appears to be in perfect health. A recent examination of the heart revealed that it is still enlarged, and the mitral murmur is still audible, but only after exercise (the exercise consisting of stepping up and down from the seat of an adult chair).

FALSE POSITIVE WASSERMANN REACTION

Subacute bacterial endocarditis should be added to the list of diseases which may cause a strongly positive Wassermann reaction. This phenomenon has been noted before by Meyer,[10] Stokes,[11] Landau and Held,[12] Corrigan [13] and Sinnbal.[14]

SUMMARY AND CONCLUSIONS

Splenectomy has been performed in 4 cases of proved subacute bacterial endocarditis (table 1, group 1). Two of these cases were my own. In 1 of them, herein reported, the patient is alive and well more than twenty months after splenectomy. Splenectomy for the treatment of subacute bacterial endocarditis has also been performed in 12 unproved cases (table 1, group 2). In the latter group 2 patients are alive and well at the time of the report; 4 patients lived from six to twelve months. In most of the cases in both groups pain was relieved, and it was the impression of most of the attending physicians that the patients had benefited from the procedure.

False positive Wassermann reactions may be obtained in some cases of subacute bacterial endocarditis.

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10. Meyer, E.: Sepsis Lenta and Positive Wassermann Reaction, München. med. Wchnschr. **74**:434, 1927.

11. Stokes, J. H.: Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, 1934, pp. 539 and 1056.

12. Landau, A., and Held, J.: Origin of Chronic, Nonvalvular Endocarditis, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:484, 1927.

13. Corrigan, M.: Nonspecific Wassermann and Agglutinin Reactions with Serum from Patients with Febrile Diseases, J. Infect. Dis. **41**:457, 1927.

14. Sinnbal, cited in Jadassohn, J.: Handbuch der Haut- und Geschleschtskrankheiten, Berlin, Julius Springer, 1929, vol. 15, pt. 2, p. 421.

MECHANICAL EFFECT OF ARTIFICIAL PNEUMOPERITONEUM AND PHRENIC NERVE BLOCK

A COMPARATIVE STUDY

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I have been using artificial pneumoperitoneum for the treatment of pulmonary tuberculosis since 1931. The applicability of this method was discussed by me in previous publications.[1] The first case of pulmonary tuberculosis in which the condition was treated by the combination of phrenic nerve block and artificial pneumoperitoneum was recorded in another paper.[2] Clinical observations showed that repeated injections of moderate amounts of air into the peritoneal cavity are capable of improving the general and pulmonary condition of some patients.[3] This is of great significance, because practically all patients treated by this measure were patients for whom artificial pneumothorax had failed to produce relief, or patients who were not eligible for other types of mechanical intervention because of age, general debility, low vital pulmonary capacity or advanced stage of pulmonary involvement. Undoubtedly, some of the benefits of this treatment were due to the fact that the intestinal tuberculosis which is so often present in cases of advanced pulmonary tuberculosis was favorably influenced by pneumoperitoneum.

Favorable symptomatic response was noted early during the course of treatment in many instances. The most impressive manifestations were lessening of the severity and frequency of cough and easier expectoration. The amount of mucopurulent material the patient was able to raise from the bronchial tract with comparatively slight effort was very gratifying. The improvement in pulmonary drainage was followed by a decrease in toxicity and a gradual disappearance of constitutional symptoms, such as chills, fever, malaise, lack of appetite and loss of weight. By the decrease or elimination of cough more

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1. Banyai, A. L.: Pneumoperitoneum in the Treatment of Tuberculous Enterocolitis, Am. J. M. Sc. **182**:352, 1931; Pneumoperitoneum, Dis. of Chest **3**:8 (Dec.) 1937.

2. Banyai, A. L.: Therapeutic Pneumoperitoneum: A Review of One Hundred Cases, Am. Rev. Tuberc. **29**:603, 1934.

3. Banyai, A. L.: Therapeutic Pneumoperitoneum, Tubercle **19**:176, 1938.

rest was secured for the lungs and quieter sleep for the patient. In 1 instance an otherwise uncontrollable pulmonary hemorrhage was checked by pneumoperitoneum. Coincidentally with the improved appetite, substantial gain in weight and strength was observed. In some instances, the sputum of patients who prior to treatment had had sputum persistently yielding bacteria became sterile. Continued treatment produced in some cases pulmonary clearing that was easily demonstrable on physical examination and on the roentgenogram. Roentgenologic evidence of the closure of rather large cavities was also observed.

For the purpose of ascertaining the mechanism of the empirically demonstrable beneficial effect of pneumoperitoneum for patients with pulmonary tuberculosis I have carried out a series of investigations. By measuring the distance between the apex of the lung and the highest point of the diaphragm before and after treatment I was able to prove that the diaphragm can be substantially elevated by repeated intraperitoneal injections of air.[4] It was shown that such elevation of the diaphragm compares favorably with that produced by bilateral surgical paralysis of the phrenic nerve. The present study has been undertaken in an attempt to find a more accurate gage of pulmonary relaxation.

An unselected group of 47 patients who were given artificial pneumoperitoneum treatment for pulmonary tuberculosis was studied. Of these, 12 had moderately advanced and 35 had far advanced pulmonary tuberculosis (according to the classification of the National Tuberculosis Association). The amount of air injected varied from 500 to 1,000 cc. at each treatment. The injections were given at weekly intervals in the beginning and at intervals of two weeks after pneumoperitoneum was well established. Roentgenograms of the chest were taken before and during treatment. Films were taken at the end of maximum inspiration and expiration, from a distance of 6 feet (1.82 meters; 182.8 cm.), with the patient in the upright position. The area of the right lung and that of the left lung were outlined by marking the upper margin of the apexes, the inner margin of the ribs and the dome of the diaphragm. The line separating the two lungs was drawn along the middle of the trachea and mediastinum. The area of each pulmonary field was measured by means of a planimeter, the tracer arm of which was carried along the circumference of the lung. The figures on the differential wheel of the planimeter indicated the areas in square centimeters.

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4. Banyai, A. L.: Radiologic Measurements of the Apico-Basal Relaxation of the Lung During Artificial Pneumoperitoneum Treatment, Am. J. M. Sc. **196**: 207, 1938.

Measurements were made in 33 instances after the first treatment, in 1 after the second, in 7 after the third, in 4 after the fourth, in 2 after the fifth, in 7 after the sixth, in 2 after the seventh, in 2 after the eighth, in 3 after the ninth, in 7 after the tenth, in 1 after the eleventh, in 3 after the twelfth, in 2 after the thireenth, in 1 after the fourteenth, in 4 after the fifteenth, in 6 after the sixteenth, in 4 after the nineteenth, in 2 after the twentieth, in 3 after the twenty-first, in 4 after the twenty-second and in 1 after the twenty-third. These represent 99 instances with films taken at maximum inspiration and at maximum expiration (and with separate measurement of the right and left lung). Including measurements of the roentgenograms studied before treatment, 584 measurements were made and analyzed.

The patients were divided into two groups. The first group included patients in whom one lung was more diseased than the opposite lung. The second group comprised patients with about equal involvement on both sides. After the first treatment the following results were found in the first group. There was no reduction in the surface area of the more involved lung on inspiration in 8 and on expiration in 8; reduction was noted in 19 on inspiration and on expiration. The maximum reduction of the surface area was 14 per cent of its original extent on inspiration and 13 per cent on expiration. Reduction was absent on the "good" side on inspiration in 5 instances and on expiration in 10; reduction was noted on inspiration in 22 and on expiration in 17. The maximum decrease was 15 per cent on inspiration and 23 per cent on expiration. For patients with about equal involvement on the two sides the maximum reduction on inspiration was 8 and 10 per cent on the right and left side, respectively, and on expiration 7 and 5 per cent, respectively. In 4 instances on inspiration and in 4 instances on expiration no reduction was noted. Table 1 gives the maximum extent of reduction of the surface area after a gradually increased number of treatments. The figures represent the highest percentage by which the preoperative surface area was reduced. Of the 33 patients studied after the first injection, repeated measurements were taken for 25 on subsequent occasions during the more advanced stages of the treatment. All patients in whom no decrease of the surface area was produced by the first injection showed decrease on subsequent injections. Table 2 gives the number of instances in which the surface area was reduced and the number of cases in which no reduction was observed.

A comparison was made between the extent of reduction of the surface area in patients with a well established pneumoperitoneum, that is, in patients who had had ten or more treatments, and that in a group of 30 patients treated by surgical paralysis of the phrenic nerve.

In the latter group the maximum reduction was 27 per cent on inspiration and 25 per cent on expiration, whereas in the cases in which pneumoperitoneum had been established the maximum reduction on the more diseased side was 36 per cent on inspiration and 35 per cent on expiration. The average reduction after surgical paralysis of the phrenic nerve was 11.7 per cent on inspiration and 7.9 per cent on expiration, whereas for patients with well established pneumoperitoneum the corresponding averages were 13.5 and 15.6, respectively. These figures

TABLE 1.—*Maximum Reduction of Roentgenologic Surface Area* *

Number of Treatments	More Diseased Lung		Less Diseased Lung		About Equal Extent of Disease			
					Right Lung		Left Lung	
	Inspiration	Expiration	Inspiration	Expiration	Inspiration	Expiration	Inspiration	Expiration
1	14	13	15	23	8	7	10	5
2	10	15	6	13	..	..	..	..
3	14	10	13	13	6	0	8	3
4	4	11	9	10	..	..	..	..
5	18	17	8	13	..	..	..	..
6	8	13	15	22	16	20	13	8
7	13	13	12	14	..	..	..	..
8	17	24	3	11	..	..	..	..
9	14	15	16	13	..	..	..	..
10	24	15	19	14	..	..	..	..
11	..	..	..	..	12	2	8	6
12	18	24	28	27	..	..	..	..
13	34†	50†	11	23	..	..	..	..
14	9	7	5	7	..	..	..	..
15	11	25	16	23	..	..	..	..
16	20	20	22	26	..	..	..	..
19	36	35	18	46	..	..	..	..
20	14	26	27	35	..	..	..	..
21	10	22	20	28	..	..	..	..
22	25	21	26	19	..	..	..	..
23	18	10	10	21	..	..	..	..

* The figures indicate the percentage by which the pretreatment surface area was reduced.
† Combined with phrenic nerve block.

show that it is possible to produce a greater reduction of the roentgenologic surface area by artificial pneumoperitoneum than by phrenic nerve block.

Assuming that the decrease in the roentgenologic surface area reflects the degree of pulmonary relaxation induced by mechanical measures and that the relaxation of the tuberculous lung is the most important therapeutic factor, it is obvious that in this respect artificial pneumoperitoneum is superior to phrenic nerve block. Additional advantages of pneumoperitoneum over phrenic nerve block are: (1) It is a reversible operation that can be adapted to the individual case or discontinued at any time during treatment; (2) the relaxation of the lung is induced gradually so that a sudden reduction of the vital capacity is avoided; (3) it causes relaxation of the "good" lung and thereby protects it against

TABLE 2.—*Number of Instances of Reduction of the Roentgenologic Surface Area*

Number of Treatments	More Diseased Lung				Less Diseased Lung				About Equal Extent of Disease								Measurements After Treatments
									Right Lung				Left Lung				
			Absent				Absent				Absent				Absent		
	Inspiration	Expiration	Inspiration	Expiration	Inspiration	Expiration	Inspiration	Expiration	Inspiration	Expiration	Inspiration	Expiration	Inspiration	Expiration	Inspiration	Expiration	
1	19	19	8	8	22	17	5	10	5	3	1	3	4	4	3	1	132
2	1	1	..	..	1	1	..	..	..	..	..	..	..	..	..	..	4
3	3	2	3	4	5	3	1	3	1	..	..	1	1	1	..	..	28
4	4	4	..	..	4	3	..	1	..	..	..	..	..	..	..	..	16
5	1	2	1	..	2	2	..	..	..	..	..	..	..	..	..	..	8
6	4	4	..	..	4	4	..	..	3	3	..	..	3	3	..	..	28
7	2	2	..	..	2	1	..	1	..	..	..	..	..	..	..	..	8
8	1	2	1	..	2	2	..	..	..	..	..	..	..	..	..	..	8
9	3	3	..	..	2	3	1	..	..	..	..	..	..	..	..	..	12
10	6	6	1	1	7	5	..	2	..	..	..	..	..	..	..	..	28
11	..	..	..	..	..	..	..	..	1	1	..	..	1	1	..	..	4
12	2	2	..	..	2	2	..	..	1	..	..	1	1	1	..	..	12
13	2	2	..	..	2	2	..	..	..	..	..	..	..	..	..	..	8
14	1	1	..	..	1	1	..	..	..	..	..	..	..	..	..	..	4
15	3	3	..	..	3	3	..	..	1	1	..	..	1	1	..	..	16
16	6	6	..	..	5	5	1	1	..	..	..	..	..	..	..	..	24
19	4	4	..	..	4	4	..	..	..	..	..	..	..	..	..	..	16
20	2	2	..	..	2	2	..	..	..	..	..	..	..	..	..	..	8
21	3	3	..	..	3	3	..	..	..	..	..	..	..	..	..	..	12
22	4	4	..	..	4	4	..	..	..	..	..	..	..	..	..	..	16
23	..	..	..	..	..	..	..	..	1	1	..	..	1	1	..	..	4
Total	71	72	14	13	77	67	8	18	13	9	1	5	12	12	3	1	396

the spread of the disease by aspiration from the opposite side; moreover, the relaxation of the "good" lung with its consequent passive hyperemia creates an unfavorable site for the development of metastatic tuberculous foci; (4) by elevating the diaphragm and supporting it in a bracelike fashion during coughing spells, pneumoperitoneum makes coughing easier, more efficient and more productive, whereas paralysis of the phrenic nerve is sometimes followed by the opposite effect; (5) by virtue of the elevation of both domes of the diaphragm, pneumoperitoneum creates a favorable condition for the healing of tuberculosis in both lungs, while simultaneous phrenic nerve block for the treatment of bilateral tuberculosis is not an accepted or a feasible operation; and (6) the curative influence of pneumoperitoneum on tuberculous enterocolitis is likely to improve the patient's ingestion and digestion, and thereby it is likely to improve his general condition, the immunity of his tissues, his resistance and his capacity for repair.

The degree of relaxation of the more involved lung was compared with that of the less involved or "good" lung. It was noted that for patients with well established pneumoperitoneum, that is, patients who had had ten or more treatments, the inspiratory reduction of the surface area on the more diseased side was greater than on the opposite side in 20 and smaller in 10; there was no reduction in 1 case, and reduction was equal on the two sides in 3. The expiratory reduction was greater on the more involved than reduction was on the less involved side in 14 cases and smaller in 16; reduction was absent in 2 and equal on the two sides in 2. Extensive pleuropulmonary adhesions, rigidity of the lung tissue caused by long standing fibrosis and contraction of the thorax were responsible for the absence of or the rather insufficient pulmonary relaxation in some cases.

An analysis of the relation between the reduction in inspiration and that in expiration in all instances showed the following data: On the right side the inspiratory decrease was greater than the expiratory in 44 instances and smaller in 42 instances; decrease was absent in 8 cases, and the values were equal in 5. On the left side, the inspiratory decrease was greater than the expiratory in 40 instances and smaller in 36; decrease was absent in 18 cases, and the values were equal in 5.

Although I am aware of the fact that two-dimensional measurements do not accurately gage changes of a three-dimensional object, such as the lung, this method is a sufficient approximation of the problem and has long been generally accepted in studies on artificial pneumothorax. Pulmonary relaxation by artificial pneumoperitoneum, as I stated before,[5] is dependent on the tonicity and integrity of the diaphragm, the tonicity

5. Banyai, A. L.: Pneumoperitoneum for the Treatment of Pulmonary Tuberculosis, in Piersol, G. M.; Bortz, E. L., and others: Cyclopedia of Medicine, Philadelphia, F. A. Davis Company, to be published.

of the abdominal wall, the type of breathing, the pathologic changes in and surgical status of the lung and the amount of air injected.

The measurements presented in this study prove that it is possible to produce a therapeutically satisfactory relaxation of the lung by artificial pneumoperitoneum. Relaxation implies a reduction of the elastic tension of the lung; this, in turn, facilitates the closure and healing of cavities. The lymph stasis in the relaxed pulmonary tissues stimulates fibrosis. The passive congestion and the increased content of carbon dioxide associated with relaxation create unfavorable conditions for the tubercle bacilli and accelerate the healing process.[6] On the basis of previous clinical investigations[7] I wish to emphasize again that in artificial pneumoperitoneum treatment, as in pneumothorax treatment, adequate relaxation of the lung is a far more important factor in healing than is immobilization. The combination of surgical paralysis of the phrenic nerve on the more involved side with pneumoperitoneum was conducive to gratifying results in my practice. It is evident that a paralyzed, flaccid diaphragm rises higher under the influence of pneumoperitoneum than does an intact diaphragm. Except when the diaphragm is fixed by heavy adhesions, remarkable pulmonary relaxation can be observed in this combined method.

CONCLUSION

Data presented in this study are based on 584 roentgenographic measurements.

It has been found that a well established artificial pneumoperitoneum is likely to cause a substantial reduction of the roentgenologic surface area of the lung and, presumably, a therapeutically satisfactory pulmonary relaxation.

Adequate pulmonary relaxation is the fundamental factor in the healing of turberculous lesions of the lung.

Empiric observations, such as the clearing of extensive lesions, checking of otherwise intractable hemorrhage and closure of large cavities in patients who were unable to take other types of mechanical treatment, postulate the attainment of sufficient pulmonary relaxation by this method.

During effective pneumoperitoneum treatment the maximum as well as the average decrease in the roentgenologic surface area of the lung was greater than that found after surgical paralysis of the diaphragm.

In these observations an explanation of the beneficial effects of this treatment is given. Because of its effectiveness and its simplicity of technic, artificial pneumoperitonuem is recommended as a useful procedure for the treatment of certain types of pulmonary tuberculosis.

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6. Banyai, A. L.: Carbon Dioxide Inhalation in Pulmonary Tuberculosis, Am. Rev. Tuberc. **30**:642, 1934.

7. Banyai, A. L.: The Respiratory Motion of the Lung During Artificial Pneumoperitoneum Treatment, Am. J. Roentgenol., to be published.

PHYSICAL AND TOXIC FACTORS IN SHOCK

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The word shock as currently used covers essentially the following conditions:

1. Primary shock, characterized by direct reduction of blood pressure and other less precisely defined acute symptoms, attributed to nervous, circulatory or toxic causes.

2. Secondary shock, a more slowly developing condition, of better defined character but of disputed etiology. It has usually been produced experimentally by mechanical, thermal or other trauma of the limbs or of the intestine. Authorities are agreed as to the epochal importance of the physical concept, established by Phemister,[1] Blalock[2] and their collaborators and corroborated by numerous writers (Herbst,[3] Holt and Macdonald,[4] Harkins[5] and his collaborators, Underhill[6] and his collab-

From the Polyclinic Hospital.

1. Phemister, D. B., and Handy, J.: J. Physiol. **64**:155-173, 1927. Phemister, D. B., and Livingstone, H.: Ann. Surg. **100**:714-727, 1934. Parsons, E., and Phemister, D. B.: Surg., Gynec. & Obst. **51**:196-207, 1930. Phemister, D. B.; Roome, N. W., and Keith, W. S.: ibid. **56**:161-168, 1933.

2. (*a*) Blalock, A.: Influence of Exposure to Cold and of Deprivation of Food and Water on the Development of Shock, Arch. Surg. **29**:1055-1068 (Dec.) 1934; (*b*) Internat. Clin. **1**:144-161, 1933. (*c*) Blalock, A., and Levy, S. E.: Am. J. Physiol. **108**:734-738, 1937. (*d*) Blalock, A., and Brooks, B.: Ann. Surg. **100**:728-733, 1934. (*e*) Beard, J. W., and Blalock, A.: J. Clin. Investigation **11**:249-265, 1932. (*f*) Daniel, R. A., Jr.; Upchurch, S. E., and Blalock, A.: Surg., Gynec. & Obst. **56**:1017-1020, 1933.

3. Herbst, R.: Arch. f. klin. Chir. **176**:98-122, 1933; Wien. klin. Wchnschr **47**:868-871, 1934.

4. Holt, R. L., in Discussion on Traumatic Shock, Proc. Roy. Soc. Med. **28**: 1473-1479, 1935. Holt, R. L., and Macdonald, A. D.: Brit. M. J. **1**:1070-1072, 1934.

5. Harkins, H. N.: Experimental Burns: I. The Rate of Fluid Shift and Its Relation to the Onset of Shock in Severe Burns, Arch. Surg. **31**:71-86 (July) 1935; Proc. Soc. Exper. Biol. & Med. **32**:432-434, 1934. Harkins, H. N., and Hudson, J. E.: ibid. **32**:434-435, 1934. Harkins, H. N., and Harmon, P. H.: Surgery **1**:276-281, 1937. Harkins, H. N.; Harmon, P. H., and Hudson, J. E.: Lethal Factors in Bile Peritonitis: "Surgical Shock," Arch. Surg. **33**:576-608 (Oct.) 1936. Harmon, P. H., and Harkins, H. N.: Peritonitis: Effect on Blood Pressure of Peritoneal Content in Suppurative and in Bile Peritonitis, ibid. **34**: 565-579 (April) 1937; Peritonitis: Effect on Blood Pressure of Protein-Free Extracts of Peritoneal Content and of Filtrates from Pure Cultures of Bacteria, ibid. **34**:580-590 (April) 1937.

(Footnotes continued on next page)

orators, Roome and Wilson,[7] Aikawa [8] and others) through demonstration of a passage of protein-containing fluid resembling blood plasma into the injured tissues, with consequent increase of corpuscle counts and reduction of volume of the blood. The opposite and older doctrine of a toxic or nervous origin has been abandoned as a sole explanation of secondary shock and is questioned even as a supplementary theory, though Cannon [9] and Dale [10] have stated their continued belief in such a factor and it has been championed in recent researches by Slome,[11] Moon and Kennedy,[12] Coonse [13] and his collaborators and others.

The earlier literature is sufficiently reviewed by Boyers,[14] Cannon [9] and the other authors cited.

Recently Dragstedt and Mead [15] have furnished apparently conclusive proof of the absence of any important amount of hypotensive substance in the blood of dogs after mechanical trauma of muscles. On the other hand, Rosenthal [16] is said to have demonstrated a substance resembling but not identical with histamine in the blood of animals after burns of the skin.

Histamine has held the place of chief interest in the chemical study of shock, and in this connection reference should be made particularly to the work of the Lewis-Barsoum group.[17] Lewis and Barsoum dem-

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6. Underhill, F. P.; Carrington, G. L.; Kapsinow, R., and Pack, G. F.: Blood Concentration Changes in Extensive Superficial Burns, and Their Significance for Systemic Treatment, Arch. Int. Med. **32**:31-49 (July) 1923.

7. Roome, N. W., and Wilson, H.: Proc. Soc. Exper. Biol. & Med. **32**:400-401, 1934.

8. Aikawa, T.: Arch. f. klin. Chir. **181**:330-336, 1934.

9. Cannon, W. B.: (*a*) Traumatic Shock, New York, D. Appleton and Company, 1923; (*b*) Ann. Surg. **100**:704-713, 1934.

10. Dale, H., in Discussion on Traumatic Shock, Proc. Roy. Soc. Med. **28**: 1493-1494, 1935.

11. Slome, D., in Discussion on Traumatic Shock, Proc. Roy. Soc. Med. **28**: 1479-1493, 1935.

12. Moon, V. H., and Kennedy, P. J.: Pathology of Shock, Arch. Path. **14**: 360-371 (Sept.) 1932; J. Lab. & Clin. Med. **19**:295-301, 1933. Moon, V. H.: Ann. Int. Med. **8**:1633-1648, 1935.

13. Coonse, G. K.; Foisie, P. S.; Robertson, H. F., and Aufranc, O. E.: New England J. Med. **212**:647-663, 1935.

14. Boyers, L. M.: Am. J. Surg. **36**:623-652, 1937.

15. Dragstedt, C. A., and Mead, F. B.: Pharmacologic Study of the Toxemia Theory of Surgical Shock, J. A. M. A. **108**:95-96 (Jan. 9) 1937.

16. Rosenthal, S. R., cited by Fantus, B., and Dyniewicz, H. A.: Compound Solution of Tannic Acid, J. A. M. A. **109**:200-203 (July 17) 1937.

17. Lewis, T., and Grant, R.: Heart **12**:73-120, 1925. Barsoum, G. S., and Gaddum, J. H.: Clin. Sc. **2**:357-362, 1936. Barsoum, G. S., and Smirk, F. H.: ibid. **2**:337-352 and 353-355, 1936.

onstrated with apparent positiveness that the phenomena of reactive hyperemia following circulatory occlusion in limbs must be due to some substance which diffuses only very slowly from its site of formation in the tissues into the blood. Barsoum and Smirk furnished evidence that true histamine or a histamine-yielding substance is increased in the blood as a result of stoppage or slowing of the circulation. They at least partially answered the objection regarding diffusibility by showing that the substance in question is held in the tissues and red corpuscles in far larger amounts than in the plasma, but it causes capillary dilatation and other typical effects only when its concentration rises in the plasma. Increase of histamine or the substance yielding it was also found in the blood of patients with extensive cutaneous burns, and the degree of this increase was approximately in proportion to the extent of the burns. On the other hand, it was not possible to correlate these chemical findings with shock symptoms or any other features of the clinical course. Up to the present, a chemical explanation of shock has not been furnished by the researches on histamine or any other substance.

Aside from surgical conditions, shocklike states are recognized medically in two principal forms: (*a*) shock occurring as a more or less acute effect of a variety of poisons, particularly histamine, bacterial products and some organ extracts, and (*b*) shock occurring as a late complication in many states of prostration or circulatory failure, which entail some degree of tissue asphyxia by reason of inadequate blood flow or possibly also direct toxic damage of the tissues or vessels. Among these states is the late, severe stage of diabetic acidosis. This observation was made possible only by the introduction of insulin, which was able to clear up the associated factors, and I was the first to state the fact that "when too long a time elapses the patient reaches a fatal stage, in which strenuous treatment may clear up sugar and acetone and raise the blood alkali, but death nevertheless occurs with symptoms resembling shock."[18] Also Wishart and I[19] first observed that dogs into which different "acetone bodies" were injected displayed only moderate symptoms of drunkenness while the poison was circulating but after its disappearance from the blood they died from increasing prostration of undefined character. Peters and his associates[20] found indications of some passage of fluid from the blood into the tissues in the presence of severe diabetic acidosis. This is in harmony with the shock

18. Allen, F. M.: Ann. Int. Med. **2**:210, 1928.

19. Allen, F. M., and Wishart, M. B.: J. Metab. Research **4**:613-648, 1923.

20. Peters, J. P.; Kydd, D. M.; Eisenmann, A. J., and Hald, P. M.: J. Clin. Investigation **12**:297-326, 1933. Peters, J. P.; Kydd, D. M., and Eisenmann, A. J.: ibid. **12**:355-376, 1933.

hypothesis.[21] Several workers have tried transfusions in the treatment of acidosis, according to current views of shock therapy, but without particularly striking results. It remains probable that any further advance in the treatment of coma must be along some line outside the ordinary routine for patients with diabetes and probably must be related to the problem of shock.

The established methods of investigating shock are open to certain criticisms. Experiments with perfusion encounter objections because of the small quantity of toxic material that may be contained in the circulating blood and the power of tissues to neutralize or destroy such material; thus it is difficult to demonstrate the nature of uremia by means of such experiments. Maintenance of arterial stasis for a few minutes, as used by Phemister and Handy,[1] is too brief to allow much accumulation of shock-producing substance. Tissue extracts may not contain sufficient amounts of the true toxin or may contain postmortem products. The usual traumatic experiments involve complications of injuries to the nervous system and also necrotic tissue and blood clot. Proof of the physical hypothesis does not disprove the existence of other factors than fluid migration and, furthermore, does not show the cause of the fluid migration. The prevailing uncertainty seems to make any innovation in the mode of attack highly desirable.

Shock resulting from asphyxia of a sufficient mass of tissue for a sufficient length of time has long been familiar to surgeons and received the notice of the Shock Committee during the World War. For example, Cannon [9a] described the case of an unwounded man who suffered merely a compression of the thigh between fallen timbers for twenty-four hours and who went into shock after being released and died in thirty-two hours. A case report by Panella [22] is similar. Experimental ligations have also been performed by Cannon, Donati,[23] Paolucci,[24] Fogliani [25] and others, with twofold results: viz., shock is

21. To guard against confusion (Atchley, D. W.: Bull. New York Acad. Med. **10**:138-150, 1934; New England J. Med. **213**:861-868, 1935), simple, precise definitions of a few fundamentals are essential. 1. Hemorrhage is loss of circulating fluid and corpuscles. 2. Dehydration is loss of fluid externally and is overwhelmingly the predominant process in the presence of cholera and of diabetic acidosis. 3. Secondary shock involves loss of fluid from the circulation into the tissues, even if the total body fluid is unchanged or increased. The radical physiologic difference is illustrated by the pyrexia of severe dehydration and the subnormal temperature of severe shock. Though the three conditions necessarily sometimes merge or lead into one another, progressive authors strive for clear differentiation, since the distinctions are important both theoretically and therapeutically.

22. Panella, P.: Ann. ital. di chir. **14**:1-14, 1935.

23. Donati, M.: Arch. ital. di chir. **12**:1-22, 1925.

24. Paolucci, R.: Arch. ital. di chir. **21**:329-344, 1928.

25. Fogliani, U.: Riv. di pat. sper. **9**:257-277, 1932.

prevented during the period of ligation of a normal or injured limb but develops after release of the ligature. The term asphyxia may be applied to the condition produced by such experiments, at least in its etymologic sense of strangulation; and though Krogh's [26] ligation of the frog's tongue in oxygen proved that a vascular reaction of hyperemia may follow even when there has been no oxygen deficit, it remains fairly certain that the disturbance of tissue respiration is the dominant factor in production of the results as described.

At a late stage in the present work, observations on this form of shock were published by Wilson and Roome,[26a] who with 19 dogs performed high ligation of one hindleg for two to twenty hours. Six of the animals survived after ligations of two to six and one-half hours; 13 died after ligations of three to thirty-six hours. For 2 animals, amputation three and one-half or three and three-quarters hours after release failed to save life. Likewise, large transfusions of blood or plasma failed to save, because exudation of fluid was increased. Death could be prevented, however, by a combination of amputation and transfusion. The loss of fluid into the tissues was proved to be similar in quantity to that which occurs with other forms of fatal secondary shock. The argument that the concentration of toxic metabolites should be greatest immediately after release, while death actually occurs many hours later, becomes inconclusive if it is assumed that these substances are mostly anchored in the tissues and are thus responsible for the outpouring of fluid both in the ligated limb and throughout the body. (Compare also the acetone body injections, Allen and Wishart.[19])

During the past eight years I have had occasion to apply elastic ligatures to various parts of the bodies (chiefly the legs) of several thousand animals, chiefly rats, for purposes to be set forth elsewhere. In the course of this work, shock was necessarily encountered, and extensive information was gained concerning the conditions of its occurrence, though the intensive studies which should have been made were impossible on account of extremely limited facilities. Nevertheless, it appears that full use has not heretofore been made of the special advantages of this method, such as the opportunity of quantitatively controlling and standardizing the degree of shock, the exclusion of nervous factors, the absence of dead tissue or blood clot, the chance for complete recovery of the animals when desired and convenience for study in general.

The procedure is as follows. A tourniquet made of one or two ordinary light rubber bands, with strings attached for tying, may be

26. Krogh, A.: Anatomie und Physiologie der Capillaren, Berlin, Julius Springer, 1924.

26a. Wilson, H., and Roome, N. W.: The Effects of Constriction and Release of an Extremity: An Experimental Study of the Tourniquet, Arch. Surg. **32**: 334-345 (Feb.) 1936.

applied to one hindleg of a rat as high as possible against the body. The pressure should be sufficient to assure absence of bleeding from incisions in the leg or from the femoral artery below the ligature, but not so extreme as to create unnecessary complications, such as thrombosis or ulceration (which require rejection of the experiment). The animal is then confined in an individual box which keeps it helpless but comfortable, with precautions against chilling. Dehydration may vary from a slight to a considerable degree. The body weight of a rat weighing 150 Gm. may fall by 10 to 25 Gm. The red blood cell count may rise by as much as 1,000,000 in five or six hours and by 2,000,000 or more if the ligation is of longer duration. Nevertheless, there is no death or serious weakness of a healthy rat during ligation, even if constriction is maintained for fifteen hours or longer. On release after a five-hour ligation the rat appears entirely vigorous; then increasing symptoms of secondary shock, in the form of subnormal temperature, dyspnea and weakness, lead to death. Strong animals are more resistant than weak ones. Old, fat rats (because of the greater mass of tissue in the thigh or because of age) are often less resistant than young, thin ones. The most important factor is the actual height of the ligature, that is, whether it remains close against the body or slips down more or less. With allowance for such variations, the degree of shock produced by three hours' ligation of one entire leg is never sufficient to kill. Ligation for four hours is often fatal, and ligation for five hours is regularly fatal.[27]

These conditions may be altered in two ways, namely extensively (by variations in the amount of tissue ligated) or intensively (by variations in duration of ligation). As an example of the former, the ligation of both entire hindlegs for three hours may be fatal; or if continued for five hours, it causes death within from three quarters of an hour to three hours after release of the ligatures, instead of the three to six hours which is usual after ligation of one leg. Increased duration intensifies the effect so that fatal shock occurs from ligation of a smaller mass of tissue. One of these factors may be used to counteract the other; for example, ligatures applied at or below the middle of the calf involve too little tissue for fatal shock. Such ligations are therefore the only ones suitable for determining the actual duration of local asphyxia which can be tolerated without the occurrence of gangrene. This is longer than commonly supposed, viz., about twelve hours for the rat and fifteen hours, or possibly more, for the dog or the cat, at ordinary room temperature.

27. Recently, with rats from another source, it has been necessary to use six hours of ligation for uniformly fatal results. It may, therefore, be necessary to establish a standard for each particular strain of rats.

Reactive hyperemia and edema have been described by former writers; and, as observed by Blalock [2] and Holt,[4] the accumulation of fluid is not limited to the ligated area but commonly extends beyond the leg, sometimes well up over the groin or the abdomen.

Since all the phenomena of secondary shock can be produced under these fairly exact and uncomplicated conditions, the method seems well suited for studying the cause or mechanism of shock. Pain and other nervous factors are eliminated, partly by the relative painlessness of the procedure and partly by the anesthesia and nerve block produced by the ligation itself. The experiments were therefore performed without anesthetics, except as specifically mentioned.

BLOOD COUNTS AFTER LIGATION

Counts were taken sometimes before application of the ligature, always just before its release and at selected intervals afterward. The blood was obtained routinely by clipping the end of the tail. In some cases of shock in which the tail yielded no blood and in other instances for comparative purposes, blood has been taken from the heart, from a jugular or femoral vein or from an artery of the leg. While the variations in different vascular tracts might be instructive for some detailed studies, the general course of dilution or concentration is shown in the same way regardless of the source of the blood. In the first part of the work, large numbers of leukocyte counts were included, which showed sometimes a relation with the concentration or dilution of the red cells but also numerous fluctuations which were meaningless for the present purpose. Hemoglobin determinations merely corroborated the red cell counts; therefore, usually only the latter were taken.

It is unfortunate that the restricted conditions under which these experiments were performed precluded determinations of blood volume, blood pressure and other important data. On this point, however, there is the complete demonstration by former writers that the rising corpuscle count is a sign of increased blood concentration, connected with loss of plasma and decrease of total blood volume.

Since the experiments were necessarily so simple and the data consist of nothing but hundreds of blood counts, it is possible to state the results summarily so as to save the space and expense of charts and protocols. Any points which may seem doubtful can be easily verified by any one interested. The basic condition is that which has been described by former authors for other species of experimental animals; namely, from a level of about 8,000,000 red cells at the end of ligation (ranging possibly from 7,000,000 to 9,000,000 according to the species and the special circumstances) the count rises steadily after release to a level of 10,000,000, 11,000,000 or 12,000,000 at death. The visibly

dark, thick character of the blood, the emptiness of all superficial blood vessels and the scanty flow even in such large veins as the femoral and jugular, occurring in parallel with the increasing local transudation of fluid and the symptoms of general prostration, conform to the full specifications of the physical hypothesis of secondary shock.

As living animals cannot be standardized as precisely as chemical reactions, exceptions and gradations occur under the aforementioned rules and are explained principally by the variable factor of constitutional strength. Animals which are weak from any cause, such as youth, age, exhaustion or intercurrent disease, are sensitive to shock in proportion to their weakness, while exceptionally strong animals have correspondingly high resistance. Several observations were made to learn whether the weak animal is unable to maintain its blood volume as efficiently as a normal animal or whether it dies from smaller changes in the blood. Ligations of limbs were found to affect the red cell counts similarly for weak animals and strong animals, but the weak ones were less able to endure the change, so that they died at an earlier stage when the erythrocyte count had risen by 2,000,000 or sometimes by only 1,000,000.

COMPARISON WITH PRIMARY SHOCK

Attempts were made to compare the blood changes of secondary shock with the effects of trauma supposed to produce primary shock. As the small size of rats renders them highly susceptible to dehydration, temperature and other influences, these experiments have all been duplicated with cats, and conclusions have been drawn chiefly from experiments with the latter. The following procedures have been used:

With the animals under amytal narcosis, nerve trunks have been dissected out (beginning at the ankle) and stimulated repeatedly by pinching and cutting from below upward in the course of several hours, until both sciatic trunks have been used up to their point of origin.

In the same or other animals, the spinal cord has been successively crushed at different levels, from its lower end to the upper thoracic region. Other animals have been kept unconscious by a series of blows on the skull.

Animals either under anesthesia or with the spinal cord divided have been subjected to bloodless traumatization of limbs or viscera, with the endeavor to avoid any marked local edema or secondary shock during this time. For example, a cat, after brief etherization for division of the spinal cord, appears entirely well except for paraplegia. One hindfoot is then amputated bloodlessly. After perhaps fifteen minutes, compression is applied to squeeze most of the blood out of another zone of tissue, and a slightly higher amputation is performed, several interlocking mass ligatures being applied to block all blood supply before the tissues are divided. These successive procedures in the course of several hours lead finally to the amputation of both hindlegs at the hips, with all connecting muscles. The cat shows no sign of pain, and each zone of tissue is removed before there is time for the preceding operation to produce much edema in it.

Blood counts taken during any of these experiments with primary shock, continued over a period equal to that occupied by experiments with secondary shock, have never shown any marked or consistent changes resembling those of secondary shock. Since the two conditions are recognized as radically different, it is questionable whether the name shock should continue to be applied to both.

Possibly the prevention of pain also serves largely to prevent shock in such experiments. But there may even be suggested a need for differentiation of the effects of certain lesions of the nervous system and tissues now lumped together under primary shock. Apparently, the sufficiently extensive mutilation of denervated tissues can cause delayed death which is not identical with death from secondary shock. It was not possible to determine in this work whether such a death is due to familiar or to unknown factors.

RESULTS OF AMPUTATION AFTER LIGATION

Regardless of the duration of ligation (up to fifteen hours or longer) if amputation is performed instead of release of the ligature, none of the phenomena of secondary shock occur. Even when both hindlegs have been subjected to prolonged ligation, the immediate amputation of both allows the animal to survive. These principles are well understood and are followed in operations on man.

When one hindleg of a rat has been ligated for five hours, amputation will still save life if performed within a variable time (the limits being about one to three hours in numerous observations) after release of the tourniquet. This is a period within which the clinical symptoms and also the rise of the blood count are still well below the maximum. If further time is allowed, until the animal has passed into a more severe stage of shock, life can no longer be saved by amputation.

These results are explainable under either the toxic or the mechanical hypothesis. Under the former the ligated leg is assumed to be a source of poison for the organism, and under the latter it is viewed as the site of fatal transudation of fluid. A nervous cause is excluded, partly by the results of amputation and partly by the complete motor and sensory paralysis which follows prolonged ligations of the legs of rats.

RESULTS OF BLOOD TRANSFUSION

Blood for transfusion is drawn from the heart into a syringe containing heparin in powder or strong solution. The animal in a condition of shock is often quiet enough to receive the injection with little restraint, but sometimes the usual veins (tail and leg) are too empty to be entered by puncture through the skin. It then becomes necessary

to etherize for injection into the exposed jugular vein, but the entire procedure occupies only a few minutes, and the rat awakens quickly without apparent harm.

For rats weighing 100 to 200 Gm., after ligation of one hindleg for five hours transfusion of 4 to 8 cc. of fresh blood ordinarily saves life within about the same time limits as amputation. Transfusion fails to save under three conditions: (1) after the lapse of too long a time following release of the tourniquet; (2) after too extensive injury, e. g., after prolonged ligation of two or four legs or of the abdominal aorta; and (3) after too intensive injury, e. g., after ligation of one hindleg for seven to twelve hours.

Under any of these conditions, however, the reviving effect of transfusion should be noted. Death from this form of shock invariably occurs by apnea, while the heart may continue to beat rather vigorously for periods varying from a few seconds up to a minute or more. This fact is in agreement with the accepted view that secondary shock is not due to failure of the circulatory organs. When respiration has definitely stopped, no matter how strongly the heart may be beating, it has never been possible in a single instance to revive the animal by transfusion or to restore respiration (for more than a few seconds or minutes) by any of the drugs or treatments in ordinary medical use. But when the rat is literally at its last gasp and in imminent danger of dying before the vein can be entered, the transfusion usually brings about an immediate spectacular improvement. Under the fatal conditions enumerated this revival is temporary; the subnormal temperature is not elevated, and extreme weakness quickly or slowly returns. Sometimes a second transfusion may give slighter benefit, but a state is soon reached in which neither transfusion nor anything else helps. The net result, therefore, is only a brief prolongation of life, ranging perhaps from half an hour to three or four hours.

The reviving effect of the transfusion can be logically explained under the physical or mechanical hypothesis as due to replenished blood volume and consequently to improved circulation. The ultimate fatality also appears explainable under this hypothesis, as follows. As regards the first condition, when the animal has reached too extreme a stage after the lapse of too long a time, this hypothesis takes cognizance of the secondary constitutional changes which have been proved to occur in the presence of advanced shock and which are necessarily fatal after they have reached a certain degree. As regards the second and third conditions, namely, the more intense injury of a given mass of tissue or the injury of a greater mass, it may be assumed that the transudation of fluid is increased, as was actually demonstrated by Wilson and Roome.[20a] In this event there may be temporary help from transfusions,

but plasma may continue to be lost until finally the circulation may be clogged with a plethora of corpuscles, and death inevitably follows.

This assumption has been tested in numerous experiments with both the second and the third condition. The amount of blood given has varied from 4 to 18 cc., the larger amounts being divided into several injections. When such transfusions are begun shortly after or even before the release of the ligature and are continued with every conceivable variation of quantity and interval, life may be prolonged by a maximum of a few hours but is never actually saved under the conditions of severe shock as mentioned. The red cell count always shows a definite increase, commonly ranging between 11,000,000 and 14,000,000, while at the same time the usual emptiness of the peripheral veins is replaced by visible distention, and at autopsy the heart and the great veins are observed to be engorged. These conditions are in accord with the supposition of an increase of corpuscles and of blood volume together with a loss of plasma.

Tests for the presence of a circulating toxin have also been made by withdrawing blood from the hearts of rats either shortly before or immediately after death from this form of shock. All the results described for transfusion of normal blood are reproduced by transfusions of "shock blood." The reviving effect is the same; a rat in the very act of dying from shock can be restored by the blood of rats which have died from shock in the same manner as by normal blood, even though the "shock blood" is thick and dark and has not been oxygenated or otherwise treated. The prolongation of life is the same whether normal blood or "shock blood" is used, and owing to individual variations it may happen that some rats receiving "shock blood" outlive some that received normal blood, in spite of the higher corpuscle and lower plasma content of the "shock blood." From these observations it seems clear that the important element in the effect of transfusions is the increased volume of the circulating medium, and that the hypothetic toxin cannot be present in more than trivial amount in the quantity of blood transfused.

RESULTS OF INJECTION OF CORPUSCLES

Corpuscles were obtained by moderate centrifugation of heparinized blood, after one or two washings with saline solution or, more often, without washing. The mass obtained was capable of flowing easily through the 26 or 27 gage needle used for all the transfusions. Experiments were performed with injections of these corpuscular sediments in various quantities and at various intervals after release of the tourniquet. The quantity tolerated is naturally less than for whole blood. Revival of dying rats may be observed to a slight extent but is often

lacking. The period of survival at best is much shorter than with whole blood, and too large or too frequently repeated injections are actually fatal. If one disregards the meaningless counts obtained when rats died almost immediately after the injection, the increase of corpuscles in rats surviving for any considerable time did not rise much above 14,000,000. All these observations accord with the idea of the importance of the physical factor of concentration of the blood and loss of plasma.

RESULTS OF INJECTION OF PLASMA

If secondary shock consists in an escape of blood plasma or a fluid closely resembling it from the vessels into the tissues, the optimum relief should logically be afforded by a restoration of plasma, as postulated by Rukstinat,[28] by Good, Mugrage and Weiskittel[29] and by most supporters of the physical hypothesis. Various experiments were performed, different amounts of tissue being ligated. In one form, 1 rat was given a transfusion of a certain amount of heparinized blood, while an equal quantity was centrifuged and divided between 2 similar rats, 1 being given the corpuscles and the other the plasma. Another plan was merely to inject plasma in the same quantities (totals of 5 to 20 cc.) at intervals, as previously described for whole blood.

For the revival of rats at the point of death from shock, the plasma (not oxygenated or otherwise prepared) was decidedly inferior to whole blood. The effect, if obtained, was slight or brief, and death sometimes actually occurred during the injection. The theoretic expectation, therefore, that plasma would produce particularly beneficial effects by filling up the circulation, reducing the high concentration of corpuscles and diminishing the viscosity was by no means fulfilled with animals in this extremely late stage of shock.

In other experiments, smaller or larger injections of plasma were given at intervals beginning either just before or soon after the release of the tourniquet, in the attempt to prevent the development of the fatal stage. The standard preparation for the majority of these experiments consisted in high ligation of both hindlegs for five hours. Three gradations of injections of plasma were then tried. In group 1 the smallest possible quantities of plasma were given (three or four injections of 2 to 4 cc. each), not preventing the concentration of blood altogether but merely keeping the corpuscle counts within the supposedly safe limits of 9,000,000 to 10,000,000 cells, the purpose being to minimize any possible harm that might be done by the injections of

28. Rukstinat, G. J.: Experimental Study of Traumatic Shock, Arch. Path. **14**:378-400 (Sept.) 1932.

29. Good, R. W.; Mugrage, R., and Weiskittel, R.: Am. J. Surg. **25**:134-139, 1934. Good, R. W., and Boyer, B. E.: J. Med. **12**:630-636, 1932.

plasma. In group 2 intermediate amounts of plasma were injected under the guidance of corpuscle counts so as to keep the concentration of the blood as nearly normal as possible from beginning to end; and in several such experiments there was success in preventing the red cells from varying more than half a million at any time. In group 3, the attempt was to overcompensate, with three to four injections of 5 to 10 cc. of plasma, so as to keep the blood constantly diluted to various degrees and to have a surplus of fluid always available for transudation.

For such a study the advantages of the ligation method are obvious, as compared with the production of shock by any means involving hemorrhage, neural lesions or the presence of masses of dead or dying tissue. Wilson and Roome's [26a] observation of the increased amount of transudation is easily confirmed, but any such increase can be amply covered by the quantity of plasma injected. It is readily understood, as shown by several authors, that when a severe reduction of blood pressure and increased blood concentration are allowed to continue for several hours the secondary disturbances are such as to prevent recovery. The advantage of the present method is that compensation for these changes can be introduced from the outset.

Under any of the three plans mentioned the circulation is sufficiently well maintained to permit of obtaining samples of blood from the tail at all stages. The third method creates visible overfilling of the superficial vessels and can be carried to the point of obviously fatal hydremic plethora. Even with this plethoric death and engorgement of the heart and the great veins at autopsy, the end still comes with apnea rather than with stoppage of the heart.

Rats with severe shock, given suitable injections of plasma from the outset, live decidedly longer than untreated controls and apparently a little longer than rats given transfusions of whole blood. The greater edema in the ligated legs is due at least partly to the longer time. The general symptoms and course of the shock are retarded but not essentially altered. The point is soon reached at which the rat with a normally maintained blood count or with a reduced blood count and appearances of increased blood volume is dying with symptoms (prostration and subnormal temperature) indistinguishable from those of the untreated rat with its concentrated blood and reduced blood volume; and further injections serve only to increase the hydremia and perhaps precipitate death.

The duration of life shows no regular parallelism with the quantity of plasma injected. Furthermore, control experiments show that the injections used in average experiments of this type can be tolerated by normal adult rats without harm.

RESULTS OF INJECTIONS OF SALINE SOLUTION

Though the foregoing experiments were favorable to the assumption of a toxic factor, it seemed advisable to give further attention to one detail of the physical hypothesis. Notwithstanding all the published papers, it may be doubted whether there is any serious deficiency of proteins or other organic plasma constituents in the presence of shock. The current hypothesis might therefore be altered to the extent of assuming that the essential feature in shock is a need for fluid in the tissues rather than a lack of plasma in the blood. Under this assumption the plasma proteins might hinder the transudation of sufficient fluid; the binding of water would be increased as the proteins became more concentrated, and thus a plethora of plasma might be practically as detrimental as a plethora of corpuscles. The unfortunate experimental conditions precluded chemical analyses to determine the actual concentration of substances in the blood, but it was possible to compare the effects of injections of saline solution with those of injections of plasma. For this purpose either Ringer solution or a simple physiologic solution of 0.85 per cent sodium chloride in tap water was used. The results were not altered when heparin was added in the same quantities as used for the transfusions.

The reviving effect of injections of saline solution (merely warmed, not oxygenated) on rats at the point of death from shock was found to be practically nil. It was even less than the effect of plasma, and the rats commonly died either during the injection or very soon afterward. Therefore, the mere increase or dilution of the circulating fluid in this terminal stage of shock was of no practical benefit.

Other experiments were performed, after the preparatory high ligation of both hindlegs for five hours, with a series of injections of saline solution similar to the previous injections of blood and plasma. Within seven hours after release of the tourniquets, several intravenous injections were given in varying amounts, ranging from 5 cc. to a total of more than 20 cc. In other experiments injections of various amounts of saline solution were given subcutaneously or intraperitoneally, alone or combined with intravenous infusions.

The resulting curves approximately duplicate two forms of curve observed after injections of plasma, the red cell count remaining nearly uniform or rising moderately. The third form of result with plasma, namely the marked dilution of the blood (provided counts are not taken within a ridiculously short time after the injection) is practically unattainable with saline solution. Illustrating the well known ease with which saline solution leaves the blood vessels, in another experiment of this type a blood count was taken simultaneously with release of the tourniquet; half an hour later 6 cc. of saline solution was injected intravenously; half an hour after that a red cell count was taken and was

more than 2,000,000 higher than the first count. Here the avidity of the tissues for fluid was apparently such as to withdraw not only the 6 cc. of injected saline solution but also a considerable amount of plasma in this short time.

If there is abnormal permeability of the blood vessels in the presence of secondary shock, it must be only in the direction of outflow. The rapid absorption of fluid which is familiar in dehydrated states is not evident in shock; and direct proof of delayed absorption was brought by Blalock [2b] for saline solution and by Daniel, Upchurch and Blalock [2f] for strychnine and phenosulfonphthalein. In the present experiments, injected saline solution remained for long periods in the peritoneum or subcutaneous tissue of animals with shock. Some quantitative idea was afforded by the fact that while an intravenous injection of 5 cc. of saline solution within three hours after release of the tourniquet has a marked influence on shock, subcutaneous or intraperitoneal injection of 5 or 10 cc. immediately after release has very little effect. With the same preparation, that is, five hours' ligation of both hindlegs, injections of 5 cc. of saline solution subcutaneously or intraperitoneally (or both) every three hours have failed to save life, though a few such injections intravenously have been effectual. In 1 extreme instance of this type, death occurred nine hours after release of the tourniquet. The original weight of the rat was 125 Gm.; the saline solution given in both subcutaneous and intraperitoneal injections amounted to 95 Gm.; the body weight of the animal at death was 205 Gm. This leaves only a possible 15 Gm. for loss through diuresis and respiration. The original red cell count at release was at a low level of 6,000,000; it rose steadily to 10,500,000 in three and one-half hours, remained approximately at this maximum for four and one-half hours, and fell slightly, so that for blood taken at autopsy it was 9,900,000. Here the large injections more than doubled the time of survival as compared with that observed for controls and probably limited the degree of concentration of the blood; but most of the fluid could be recovered from the peritoneum and subcutaneous space at autopsy, and death occurred with typical symptoms. In a few instances, the rats being presumably very strong, life was saved by large intraperitoneal and subcutaneous injections given early and repeated after some hours. In general, such injections are most useful as a convenient supplement to the intravenous injections. One or two small intravenous injections keep the animal alive long enough to allow time for the early subcutaneous or intraperitoneal injections to become effective, and thus the trouble of prolonged watching and repeated intravenous injections may be saved. It may also be assumed that this method involves less sudden and extreme fluctuations in concentration of the blood than must occur with large intravenous injections. Any other superiority of this method has not been

perceptible; also, a harmful effect of the intravenous injections in washing protein out of the vessels is not indicated by any symptoms.

The animals into which saline solution was injected as a group exhibited the greatest edema of all, owing partly at least to the longer period during which ligation was maintained. This edema, spreading beyond the ligated legs as usual, sometimes extended over the surface of the abdomen, halfway up to the axilla.

Injections of saline solution are effectual in proportion as they are given early after the release of the tourniquet. As has been mentioned, they are useless for an animal at the point of death. Injections at intermediate periods give intermediate results, sometimes saving life but more often prolonging it greatly without saving it. In a number of instances, when injections were begun two hours or more after the release or when they were begun promptly but in too small amount, it has been possible to keep the rat alive in a constantly weak condition until some time the next day by watching it all night and giving intravenous injections of saline solution every few hours, so that the red cell counts were kept approximately uniform. The most extreme example of this kind was presented by a strong young rat weighing 120 Gm. Ligation of both hindlegs was maintained for five hours. Owing to the fact that the ligatures slipped down a little, the animal at three and one-half hours after release was not in immediate danger, though too weak to turn over when placed on its back. The red blood cell count had risen from 8,000,000 to 11,500,000, and at this point treatment was begun with an intravenous injection of 5 cc. of saline solution. Strength was improved, and the erythrocyte count one hour later was found reduced to 9,750,000. By six repetitions of the same injection at suitable intervals this animal was kept alive for fifty-two hours from the time of release, while the red cell count was kept between 9,000,000 and 7,000,000 throughout this time. All such deaths may be explainable under the accepted doctrine that when the secondary constitutional changes produced by shock have reached a certain stage they progress fatally in spite of any treatment.

The most important result of these experiments was the discovery that early and adequate injections of saline solution afforded a means of regularly and permanently saving the lives of rats under conditions of otherwise hopeless shock. Without treatment, ligation of one hindleg for five hours was invariably fatal, but the injections saved life after ligation of two legs for five hours. In dozens of attempts with various methods, this result had not been accomplished in any instance by injections of blood or plasma. This result, while it demonstrated the importance of the physical factor of the simple shift of fluid even in this severe form of shock, also suggested that the most important condi-

tion is a need of the tissues for fluid. Apparently the investigators or surgeons who have complained that saline solution leaks out uselessly from the vessels have not given sufficient quantities to determine whether the final result is drowning of the organism or establishment of an equilibrium. The latter proves to be true, at least under the conditions of these experiments. The chief purpose of therapy, therefore, is to give not a fluid which will remain in the vessels but one which will pass readily out of the vessels. These experiments did not include tests of the permeability of vessels and therefore do not disprove the possible existence of abnormal permeability. But when saline solution is given from an early stage in sufficient amount to satisfy the avidity of the tissues, the supposed abnormal permeability of the vessels does not prevent the plasma from remaining in them without difficulty. These conditions are radically different from those of hemorrhage. Also there is no trouble from lack of proteins or other substances, and the body can evidently supply every element that is needed except water and probably sodium chloride. These findings are in accord with the empiric practice of most surgeons, who depend chiefly on large quantities of fluid for treatment of all conditions involving shock.

ACACIA

For comparison with the injections of plasma, a smaller number of experiments were performed with injections of acacia.[30] Whether made up with water or with physiologic solution of sodium chloride, the acacia solution gave results distinctly inferior to those with plasma and in some instances seemed definitely to hasten death, especially when large quantities were used. This experience harmonizes with the view (Walker and Keith,[31] MacFee and Baldridge [32]) that anything hindering egress of water from the vessels is harmful rather than helpful in cases of shock.

ABDOMINAL LIGATIONS

One of the aforementioned methods for increasing the severity of shock consists in extending the asphyxia over a larger area. This plan provides either an enlarged field of transudation or a greater mass of tissue to produce toxin, according to one or the other hypothesis.

Trials were therefore made with temporary occlusion of the abdominal aorta at various levels below the renal arteries. In such a small animal as the rat the result is accomplished better by a tourniquet around the unopened abdomen. If the rat, completely relaxed under ether, is held vertically with the head down, the viscera drop toward

30. A 6 per cent solution of acacia was employed, prepared from the concentrated ampules acacia without sodium chloride of Eli Lilly & Co.

31. Walker, M. A., and Keith, N. M.: Am. J. Physiol. **95**:561-672, 1930.

32. MacFee, W. F., and Baldridge, R. R.: Ann. Surg. **100**:266-278, 1934.

the diaphragm so as to leave space for making several turns of a heavy rubber band around the lower part of the abdomen, stopping circulation completely.

The early effect of release of the ligature is a much more severe degree of shock than follows ligation of the hindlegs with a slighter degree of reactive hyperemia and edema of the ligated parts. The extreme limit of endurance is one and one-half hours; an exceptional rat may survive if the tourniquet has been placed very low, but the majority die within a few hours after release, with the typical rising curve of blood counts. Ligation for two hours has proved invariably fatal not only for untreated rats but for rats treated with transfusions of blood or plasma.

The later effects of nonlethal ligations of one-half hour or longer are: (1) paraplegia, clearing up within a few weeks; (2) paresis of the lower part of the bowel, usually only to the extent of transitory abnormality of defecation but sometimes fatal; and (3) retention of urine with dribbling, presumably due to prostatic swelling together with vesical paralysis. No attempt has been made to catheterize, and every male rat has died within nine days at most from hydronephrosis and presumably uremia. The method may therefore be of interest to persons desiring to produce such a condition experimentally. This difficulty was overcome by changing to female rats, which ordinarily recover after a few days of dribbling of urine. Also, the large size of the testes of adult male rats makes dangerous addition to the shock when ligations of long duration are used.

A series of female rats were subjected to such ligations for the fatal period of two hours. It was found possible to relieve the shock and obtain complete recovery by giving injections of saline solution, which checked the rising red cell counts in practically the same manner as with the ligation of the two hindlegs. Recovery occurred, that is to say, provided the intravenous injections were begun very early, alone or in combination with subcutaneous or intraperitoneal injections. The latter injections were never adequate without the intravenous injections. Also, the intravenous injections did not save life when started at a late stage, even though the corpuscle counts were reduced to normal.

These experiments showed that the compensation for displacement of fluid by means of injections of saline solution succeeds in controlling even shock resulting from asphyxia of extensive portions of the body. Under these conditions also, saline solution is superior to blood or plasma.

RESULTS WITH INTENSIFIED SHOCK

Abdominal ligations of the type described, continued for three or four hours, are invariably fatal regardless of any treatment, even though the measures employed may prevent increased blood counts.

Ligation of all four legs of a rat close against the body for five hours or longer was uniformly fatal in several trials. With this type of ligation also the blood count can be kept approximately normal by suitable injections of saline solution, but death occurs nevertheless.

For comparison, all four legs of a strong dog weighing 10 Kg. were ligated with heavy rubber bands for seven hours with the dog under amytal narcosis. Marked dyspnea began almost immediately after release and increased, with prostration, to death in one and one-half hours, while the red cell count rose by over 2,000,000. The legs of dogs and other large species do not flush and swell as rapidly as do those of rats after long ligations, and within the time mentioned the paws had scarcely become warm, and local edema was barely perceptible. It seemed obvious that the loss of plasma indicated by the blood counts must have occurred elsewhere than in the ligated parts. Also, considering the resistance of dogs to hemorrhage, it is scarcely conceivable that the precipitate symptoms and early death could have been due either to vascular dilatation or to migration of fluid in the ligated limbs.

With regard to the aforementioned examples of ligation of extensive masses of tissue it is possible to raise a question of nervous influence, gross circulatory disturbance, visceral injury (in the case of abdominal ligations) or other complication in addition to the pure shock. Clearer conditions may be obtained by making the injuries intensive rather than extensive. It is thus ascertained that the high ligation of one hindleg for eight to ten hours is inevitably fatal in spite of any treatment.

In such animals, the rise of the blood count can be controlled by the same amounts of injected saline solution which have been described as being life saving for animals with milder shock. At the same time, an adequate blood volume is indicated by the visible fulness of the superficial vessels and the easy flow of blood from the clipped tail. Larger injections of saline solution or supplements of any quantity of blood or plasma do not improve the results, even though carried to the point of distention of all visible vessels and engorgement of the heart. The difficulty is not in maintaining the desired volume and concentration of the blood but in the fact that the rats die in spite of treatment, with typical symptoms of shock. On the other hand, it may be recalled that after ligation of one or both hindlegs for even more than ten hours life can still be saved by sufficiently early amputation.

After a properly performed ligation maintained for such periods there is neither thrombosis nor gangrene, the limits of endurance of asphyxia by the local tissues being reached several hours later. Release of the tourniquet is followed by intense hyperemia and edema within a few minutes in the rat, and within a longer time in larger species. But as the period of survival after ligations of eight to ten hours' duration

is decidedly shorter than after ligations of four to five hours' duration, the resulting edema is less in the legs ligated for the longer period, and there is less extension to the adjoining parts of the body. This point came to notice too late in the present investigation to permit of making a statistical comparison of the weights of legs after long ligation with those subjected to shorter ligations in the earlier work, but the results of simple inspection seem sufficiently plain. The purely physical hypothesis, therefore, meets this obstacle, that the more severe and fulminant is the shock the slighter is the extent of local migration of fluids.

The factor of local vasodilatation may be discussed as follows: (1) It is not appreciably greater, according to gross observations, in a limb ligated for ten hours than in one ligated for five hours; (2) it has been found to show its most powerful effect in reducing blood pressure soon after release of the ligature, whereas death occurs considerably later, and (3) it is inconceivable that this factor should be as great in an animal with one leg ligated for ten hours as in an animal with two legs ligated for five hours, yet the experiments show that the latter animal can be saved by injections of saline solution while the former cannot.

Therefore, unless persons more fortunately equipped, with facilities for continuous instead of intermittent injections, and for determinations of blood volume and blood chemistry and other direct data, are able to alter these facts or their interpretation, the only possible conclusion must be in favor of a toxic substance as the fundamental etiologic factor. Presumably the asphyxiated limbs will offer rich material for chemists seeking to identify this substance.

Although the symptoms become more severe and rapid as the time limit entailing tissue necrosis is reached and passed, they do not seem to differ in essential character from the results of ligations maintained for briefer periods, at least according to superficial appearances. It is therefore possible that no essential complication has been introduced in previous work, most of which has been done with shock of complicated causes, namely that produced by mechanical trauma, by burns or by freezing. With such injuries, clinical or experimental, at least three sources of disturbance are conceivable, aside from a nervous factor; first, the absorbed products from dead tissues or blood clot; second, the products of tissues damaged but not killed, and third, the physical factor of fluid migration, represented by edema in the adjoining parts. The possibility is open that the shock-producing substance derived from asphyxiated, traumatized, dying or dead tissues is one and the same, or that there is a series of related substances having similar effects. The accurately controllable gradations of local asphyxia offer a means of deciding such questions.

An additional argument may perhaps be furnished by more detailed study of an observation which was made only cursorily; namely, application of a loose tourniquet (so as to produce suitable obstruction of veins without cutting off the arterial inflow) results in edema which apparently may be greater than that which follows tight ligation, and yet the rats survive the loose ligation for six to twelve hours with little or no sign of shock.

THERMAL INFLUENCES DURING LIGATION

The following are a few pertinent facts taken from another phase of the investigation, to be published elsewhere: Elevations of temperature of various grades up to 41 C. increase the effects of ligation and shorten the time for which it can be endured. Oppositely, reductions of temperature diminish the effects. Thus, when the ligated parts are refrigerated by being kept immersed in ice water, the otherwise surely fatal ligations of the hindlegs for eight hours and of the abdomen for three hours can be carried out safely; the changes in the blood are minimized, and recovery is readily obtained. While it is evident that hyperemia and edema are augmented by heat and reduced or retarded by cold, the facts previously stated turn one's attention predominantly to metabolism in the tissues. It appears most probable that the metabolic processes which give rise to the shock toxins in asphyxiated tissue are accelerated by heat and inhibited by cold. These experiments also reproduce all the mechanical disturbances, together with the subsequent paralyses and visceral damage, described for the most extensive ligation experiments, and they therefore prove that these disturbances are not responsible for the fatal results. Furthermore, the special mode of confinement and the methods necessary for guarding against fall of the body temperature entail greater general strain on the organism than does simple ligation.

OTHER THERAPEUTIC ATTEMPTS

Orientation experiments were performed with several methods other than injection of fluids, partly for comparison with the known results in other forms of shock and partly for light which they might throw on the nature of the condition.

The fall of rectal temperature, often below 30 C., is more marked in rats than in larger animals. This fall occurs when rats are allowed to suit their own comfort, usually by huddling among other rats in a cage. Chilling accentuates the fall of temperature and apparently hastens death slightly, as is supposed to be true of the human being. Attempts to keep the temperature normal or to raise it after it has fallen by placing the animal on a heated surface or in a warm air chamber or a warm bath produce signs of discomfort in the animal and decidedly hasten death.

Injections of various doses of dinitrophenol were also given, with a view to raising temperature by increasing oxidation in the protoplasm. Doses large enough to have any perceptible effect hastened death.

On account of the dyspnea and especially because of the very dark blood in later stages, oxygen was administered, without success.

Dextrose was tried subcutaneously and intravenously, because of its status as a food and as a cardiac stimulant, and also because of the recommendations for its use in human shock by several authors (cf. also Mazzola and Torrey [33]). The artificial hyperglycemia thus produced seems to be not only useless but distinctly harmful in this form of secondary shock in rats.

Results of a few attempts with sodium bicarbonate, suggested by the dyspnea and also by the possibility of the presence of acid products derived from the asphyxiated tissues, were not encouraging.

Injections of hypertonic saline solution, made with a view either to restoring circulatory electrolytes (Gilman,[34] Doménech-Alsina [35]) or as a possible relief for central nervous edema which might be responsible for the terminal apnea, likewise failed to improve results.

Crude trials of epinephrine hydrochloride were without benefit. Also, though stress has been laid on the suggestive resemblance between secondary shock and deficiency of the adrenal cortex (Swingle and his collaborators; [36] Heuer and Andrus; [37] criticism by Freeman [38]), a commercial preparation (eschatin), given in the attempt to save rats which had reached the late, fatal stage of shock, seemed useless in small doses and probably harmful in large doses. (I found it also unavailing for a diabetic patient in the terminal stage of coma.)

Attempts to produce either habituation or immunity to the supposed toxin, by subjecting rats to repeated ligations of various amounts of tissue at various intervals during a number of weeks, definitely failed to make them more resistant than untreated rats.

In a series of rats which had undergone ligation of legs for sufficient periods to assure fatal degrees of shock, a variety of attempts were made with subsequent refrigeration of the limbs (preserving warmth of the body) for the purpose of retarding the hyperemia and edema or the absorption of toxic material in the asphyxiated tissues.

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33. Mazzola, V. P., and Torrey, M. A.: Am. J. Obst. & Gynec. **25**:643-653, 1933.

34. Gilman, A.: Am. J. Physiol. **108**:662-669, 1934.

35. Doménech-Alsina, F.: Rev. de cir. de Barcelona **4**:369-383, 1932.

36. Swingle, W. W.; Pfiffner, J. J.; Vars, H. M.; Bott, P. A., and Parkins, W. M.: Science **77**:58-64, 1933. Swingle, W. W., and Parkins, W. M.: Am. J. Physiol. **111**:426-439, 1935. Parkins, W. M.; Taylor, A. R., and Swingle, W. W.: ibid. **112**:581-590, 1935.

37. Heuer, G. J., and Andrus, W. D.: Ann. Surg. **100**:734-741, 1934.

38. Freeman, N. E.: Science **77**:211-212, 1933; Ann. Surg. **101**:484-493, 1935.

with the hope that a more gradual onset of shock might favor the resistance and survival of the animal either spontaneously or with the aid of transfusions or saline injections. No encouragement was gained in this direction.

Also, in the later stages of shock, whether or not the animals had been given transfusions or injections of saline solution, all four legs were ligated close against the body in order to cut off the most distant vascular tracts in which stagnation may most readily occur and to allow all the circulatory, nervous and hormonal resources to be concentrated in the trunk and head, in an effort to save life at sacrifice of the limbs. This also proved harmful rather than helpful.

The conclusion may be quoted in the words of Mann and Essex:[39] "When the tissues of the body have been subjected to an inadequate flow of blood for too long a period of time, no treatment yet devised will save life."

COMMENT

It is possible to distinguish theoretically three entities included in the present interpretation of the word shock. One of these is the neural injury, which may partly be defined as to anatomic lesions and physiologic effects, such as reduction of blood pressure, and may appropriately be covered by the term shock, because of its vagueness and because of the logical relation to the original meaning of the word.

The second is the other element which is often assumed to exist in primary shock, namely, an influence of the injured tissues apart from the nervous injury. Neither the nature nor the actual existence of this element has been positively demonstrated, but it should be subject to investigation in tissues separated from their nerve connections, and the part played by circulatory factors, dehydration, temperature, infection, tissue toxins or anything else should be definable.

The third is the condition now called secondary shock; and since this is recognized as being entirely different from primary shock and also is a departure from the everyday meaning of the word shock, a replacement of this clumsy designation by something more definite seems desirable. While the evidence obtained in the present investigation is unfortunately only indirect, it at least suggests some such provisional name as histotoxicosis. The vasomotor and other phenomena may thus be conceived as resulting from nervous and humoral agencies, which supplement each other as in so many other physiologic processes. This hypothesis at least offers a rational explanation of the entire range of events, classifiable in three degrees: (1) injury such as a small contusion or burn, in which the combined nervous vasodilatation and histotoxin production cause only local redness and swelling without

39. Mann, F. C., and Essex, H. E.: Am. J. Surg. **28**:160-165, 1935.

appreciable constitutional effects; (2) more extensive damage, involving primary general vasomotor disturbances of nervous origin and the formation of greater quantities of histotoxin, which not only augment local transudation but also escape into the circulation and set up similar processes throughout the body (this loss of fluid, however, can still be compensated for by administration of sufficient fluid); (3) still more extensive or intensive damage, in which either the primary nervous disturbance or the secondary production of histotoxin may be fatal in spite of preservation of the fluid balance at all stages.

The final demonstration and designation must be left to the chemist, who may be able to identify the hypothetic histotoxin. Local asphyxia may be regarded as the ideal method for this study, because of the simple and accurate control, exclusion of the nervous factor by the ligation, absence of dead or dying protoplasm, avoidance of other complications and possibility of full recovery of the animals when desired. There may even be conjecture whether the condition of secondary shock, or histotoxicosis, uniformly originates from asphyxia, in the sense that injuries may disturb cell respiration. Regardless of this speculation, the proved fact that this condition can be caused by tissue asphyxia supports the opinion that a variety of conditions, including infection, intoxication, hemorrhage, dehydration, circulatory or respiratory failure or any prostration severe enough to cause a certain deficiency of blood supply in any part or throughout the body, may give rise to asphyxial histotoxicosis, and that the clinical difficulty of distinguishing these states sharply from the so-called secondary shock may be due to an essential and inevitable mingling of the conditions.

SUMMARY AND CONCLUSIONS

1. As former authors have shown, the most distinctive characteristic of secondary shock is the increased concentration and reduced volume of the blood, caused by migration of fluid into the tissues, and the changes in red cell content are the most quickly and easily ascertained index of this process. Temporary local asphyxia of limbs or other tissue masses appears to offer the best experimental means for producing this condition, because of its simplicity, its accuracy of control, its freedom from complication by tissue necrosis and other conditions and the opportunity it affords for studying various details.

2. Traumas which typically produce primary shock, repeated during a period equal to that within which secondary shock is able to manifest itself, fail to cause the characteristic blood changes of secondary shock, thus corroborating the view that the two conditions are radically different. Circumstances did not permit of determining whether any other primary effect can arise from mutilated tissues, for example, after denervation.

3. The effects of local asphyxia, as regards both changes in the blood and the attendant symptoms and death of the animals, can be prevented by sufficiently early amputation of the asphyxiated parts, as is already known of similar operations on the human being. Amputation does not save life at a later stage, after more advanced changes in the blood have occurred.

4. The following therapeutic observations have been made with various methods of replacement of the migrated fluid:

(*a*) Animals at the point of death may be strikingly revived by transfusions of whole blood, while separated corpuscles or plasma have less value and saline solution has practically none. Such recovery is always brief, and no amount of the fluids mentioned actually saves life at this stage.

(*b*) Death, which regularly occurs under certain standard conditions, e. g., after five or six hour asphyxia of one hindleg of a rat, is preventable by early transfusions with blood or plasma, not with corpuscles. These results, and those under *a*, agree fully with the clinical evidence of the value of transfusions of blood or plasma to compensate for loss of circulating fluid under certain conditions in shock. An equivalent benefit by acacia solution [40] was not demonstrable.

(*c*) The results mentioned under *a* and *b* are obtained practically as well with the blood of animals dying in shock as with normal blood. This disproves the existence of any considerable amount of toxin in the circulation.

(*d*) After asphyxia of extensive masses of tissue, transfusions of blood or plasma no longer suffice to save life, even though the corpuscle count is kept at a normal or reduced level and all indications point to normal or increased blood volume together with adequate propulsion of the blood. Theories which regard these as the determining factors in shock are thus invalidated.

(*e*) In the conditions described under *d*, simple injections of saline solution are able to save life when plasma fails. It is deduced that the essential physical factor is the obligatory edema or avidity of the tissues for fluid, and that the most important requisite in treatment is a fluid which will pass easily out of the vessels to satisfy this need. When this is supplied, the plasma automatically remains in the vessels. The composition of the blood and the animal's life are preserved, notwithstanding abnormal permeability of the vessels or other supposed changes.

(*f*) After more intensive, i. e., more prolonged asphyxial injury of tissues, death occurs in spite of injections of saline solution which

40. Stanbury, J. B.; Warweg, E., and Amberson, W. R.: Am. J. Physiol. **107**: 230-236, 1936.

prevent rise of the corpuscle count and maintain the gross appearances of adequate filling and circulation in the vessels. It seems possible that the composition of either the blood or the tissues is altered to fatal degree.

(*g*) Various therapeutic attempts along other lines than fluid replenishment have failed, so that the physical hypothesis must be credited with suggesting the only helpful form of treatment.

5. The effects of local asphyxia, as regards changes in the blood, symptoms and death, are augmented by heat and inhibited by refrigeration of the parts during asphyxia.

6. On the basis of the evidence in favor of the toxic hypothesis, it is suggested that a substance or substances derived from the injured protoplasm may be a highly important factor affecting the vascular permeability, edema formation and other symptoms. The usefulness of such a term as histotoxicosis is therefore provisionally suggested.

KRUKENBERG TUMOR

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In 1896 Frederick von Krukenberg described a rare type of ovarian tumor of which he had seen 5 instances. The tumor presented certain characteristics of form and growth not seen in other ovarian tumors. It affected both ovaries and was solid; it was actually accompanied by ascites and was free from adhesions. Histologically it had a fibrosarcomatous-appearing stroma which enclosed large cells with a mucoid-like protoplasm. Often these cells had a nucleus displaced to the periphery, which gave them a "signet ring" appearance. Von Krukenberg believed the tumor to be a form of sarcoma and christened it "fibrosarcoma ovarii mucocellulare." The comparative rarity of the Krukenberg tumor is shown by the scant number which have been reported in the medical literature. Masson [1] in 1934 reported 5 cases observed at the Mayo Clinic from 1909, although he stated that in earlier files there are records of other tumors which might have been Krukenberg tumors. By 1918 Major [2] was able to collect reports of 54 cases, to which he added the report of a case of his own. In 1929 Fallas [3] reported 23 additional cases, including 2 of his own. In 1930 Hundley [4] brought the number to 102, and since then, up until 1934, 3 cases have been reported in American literature and 10 in foreign journals. The foregoing summary is taken from the work of Andrews,[5] who with 3 cases of his own brought the total number of reported cases to 118 in 1934. Since then, several cases have been reported both in this country and abroad.[6]

From the service of Dr. E. MacD. Stanton and Dr. Charles W. Woodall, Ellis Hospital.

1. Masson, J. C.: Krukenberg Tumors of the Ovary, Am. J. Obst. & Gynec. **27**:825, 1934.

2. Major, R. H.: A Study of the Krukenberg Tumor, Surg., Gynec. & Obst. **27**:195, 1918.

3. Fallas, R.: Krukenberg Tumor of the Ovary with Report of Two Cases, Surg., Gynec. & Obst. **49**:638, 1929.

4. Hundley, J. M., Jr.: Krukenberg Tumors and Other Secondary Ovarian Carcinomas, South. M. J. **24**:579, 1931.

5. Andrews, C. J.: Krukenberg Tumor of the Ovary, South. M. J. **27**: 597, 1934.

6. Armstrong, M. V., and Wolfe, S. A.: Krukenberg Tumor of the Ovary, Am. J. Obst. & Gynec. **27**:906, 1934. Horsley, J. S., Jr.: Krukenberg Tumor of the Ovary, South. Med. & Surg. **96**:272, 1934. Runyeon, F. G.: The Krukenberg Tumor, J. A. M. A. **103**:1199 (Oct. 20) 1934. Comando, H. N.: Krukenberg Tumor of the Ovary, Am. J. Surg. **26**:575, 1934. Fennel, E. A.: Krukenberg Tumor, ibid. **30**:376, 1935.

Although at the time of this writing the total number of reported cases still remains well under 150, there is fairly voluminous literature on the subject. Of particular interest in this literature is the question of pathogenesis. It is generally conceded that the ovarian tumor is a secondary or metastatic growth, the primary lesion of which occurs most frequently in the stomach but occasionally in the intestines or in the gallbladder. It is entirely possible that the few tumors which were thought to be primary growths in the ovaries would have turned out to be secondary had a careful enough search been made at postmortem examination. This possibility is illustrated in the case reported by Major,[2] who discovered the primary growth only after studying serial sections of the stomach. In most cases in which autopsy has been done, observations have shown the primary growth to have been elsewhere than in the ovaries. Jarcho [7] reported 7 cases of Krukenberg tumor; 6 of the lesions were proved at autopsy to have arisen from a primary growth in the stomach. In the seventh case autopsy was not performed.

The mode of metastasis from the stomach or intestines to the ovaries opens up an interesting field of speculation. At least three theories have been suggested, as follows:

1. Implantation from malignant cells cast loose from the parent growth, which have floated through the abdomen and become attached to the ovaries. This theory can be dismissed without too much credence because of the medullary nature of the ovarian growth. The serous capsule is not involved except by extension from within.

2. Extension through the blood stream. One does not ordinarily think of carcinoma metastasizing through the blood stream, but there are certain features about Krukenberg tumors with other associated metastases which justify some belief in the hematogenous theory. Jarcho [8] in a recent publication has shown most interestingly the close relation between lymphangitic carcinomatosis of the lungs, metastatic infiltration of carcinoma in bone marrow and Krukenberg tumors, all of which arise most often as secondary manifestations of a flat, infiltrating scirrhous carcinoma of the stomach. He pointed out that the metastases to the lungs can be accounted for by retrograde dissemination along the lymphatics from the hilus toward the pleura, but that actually tumor cells are occasionally found in the blood vessels of the lungs as well as in the lymphatics. This could be accounted for by the passing of tumor cells from the thoracic duct into the blood stream. As regards the bone marrow, hematogenous metastasis seems to be the only explanation, as up to the present time no lymphatics have ever been demonstrated in bone marrow.

7. Jarcho, J.: Krukenberg Tumors and Their Practical Problems, Am. J. Obst. & Gynec. **13**:288, 1927.

8. Jarcho, S.: Diffusely Infiltrative Carcinoma, Arch. Path. **22**:674 (Nov.) 1936.

3. Retrograde metastasis along the lymphatics. This is the theory which seems to have the widest support. It suggests that there has been an early blocking of the lymphatic reservoir. The frequent association of ascites with Krukenberg tumors would be explained by this theory.

In the light of the recent work reported by Jarcho [8] it seems questionable that the Krukenberg tumor is a separate entity. It seems, rather, to be one expression of diffusely infiltrative carcinoma occurring in women, in whom the predominant metastases are in the ovaries.

REPORT OF A CASE

The following case is one of a Krukenberg tumor of the ovary with primary growth in the stomach, as proved by autopsy.

History.—Mrs. R. D., an Italian woman aged 30, came to my office on Jan. 16, 1937, complaining of backache and of pains in the pelvis. There was no definite date of onset, but there had been a gradual increase of painful symptoms. She had no urinary trouble. The menstrual function was somewhat irregular; menstruation would occur at intervals of anywhere between twenty and thirty days. The bowel movements were irregular. There was a moderate vaginal discharge. At times, bending would cause severe abdominal pain and nausea. The past history was not notable. The patient had had three children, the youngest being 5 years of age. She had had no miscarriages.

Examination.—Physical examination showed a well developed woman of excellent color. The head and neck were normal. The heart and lungs were normal; no audible rales were found. The pulse rate was 100; the temperature was 99.6 F. The abdomen was somewhat distended; generalized tenderness was present over the lower half. The patient was very obese, and a considerable amount of free fluid was present in the abdomen, so that abdominal palpation and bimanual pelvic examination were not particularly enlightening. However, there was marked resistance in the lower part of the pelvis, and it was thought that some mass could be felt in the right fornix. Urinary examination showed a specific gravity of 1.028, with no albumin or sugar; microscopic examination showed nothing pathogenic. The patient was sent to the Ellis Hospital with a tentative diagnosis of an inflammatory condition of the pelvis, based on the tenderness in the pelvis accompanied by moderate fever and on a history of five years' sterility. As she was first seen on a Saturday afternoon and had no acute symptoms indicating immediate operation, a laparotomy was scheduled for the following Monday morning. Early on Monday morning she noticed an acute pain in the pelvis. She was brought to the operating room at 8:30. Before operating, I noticed that there was considerable increase in the size of the abdomen, apparently caused by the volume of free fluid.

Operation.—The operation was performed with the patient under cyclopropane anesthesia. A low median incision was made. When the peritoneum was opened several quarts of straw-colored free fluid escaped, and a solid tumor of the right ovary presented itself. It was somewhat hemorrhagic in appearance and was edematous, with dark purplish areas on the peritoneal surface. The tumor was free from adhesions and was completely twisted on its pedicle, through 365 degrees.

The tumor was approximately 6 inches (15 cm.) in diameter. The left ovary, while slightly enlarged, did not present any definite gross abnormality. After the intestine had been packed back, numerous flat, grayish patches scattered along the course of the lower part of the sigmoid flexure of the colon and the upper part of the rectum were observed. No similar patches were noticed through the lower part of the abdomen. Palpation of the upper part of the abdomen did not reveal any nodules on the surface of the liver, in the stomach or in other neighboring structures. The right ovary was excised. In addition, both tubes were removed to prevent possible pregnancy in a patient who obviously was suffering from a carcinoma of the ovary with metastases. The whole operation consumed thirty-five minutes, and the patient's condition was excellent both during the operation

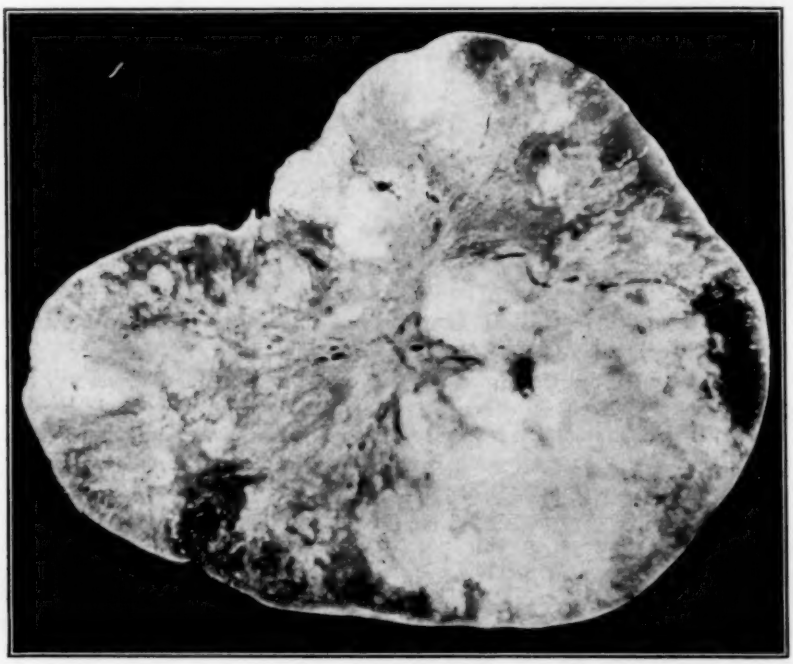

Fig. 1.—Photograph of the cut surface of the right ovary (reduced).

and at its close. The highest pulse rate was 96. During the day of the operation (January 18) and on the morning of January 19 her condition was entirely satisfactory. The highest temperature on the evening of the operation was 99.6 F., and the highest pulse rate 92. The next morning the temperature was 98 F. and the pulse rate 86. During that night, however, something happened to induce a fever, and the next morning the temperature was 102.6 F. and the pulse rate 100. By night the temperature was 104.4 F. and the pulse rate 126. From that time on there was a steady but gradual rise in pulse rate and temperature until the time of her death on January 25, when the terminal temperature reached 108 F. and the pulse became uncountable. During all this time the respiratory rate remained below 30, and there was no evidence of pulmonary involvement. There was some gaseous distention of the abdomen accompanied

by dilatation of the stomach and occasional vomiting. This was fairly well controlled by the use of gastric lavage and the Levine tube. Hypodermoclysis several times as well as proctoclysis supplied the patient with body fluids. During all this time there was no evidence of intestinal obstruction, nor did I believe that there was any real peritonitis, as the abdomen, despite some distention, was soft and not tender. The patient died at 1:30 a. m. on January 25.

Pathologic Report.—The pathologic report on the operative specimens showed the right ovary to be a flattened oval mass 15 by 11 by 6 cm., weighing 625 Gm. The entire serosa was smooth except for a small area to which the pedicle was attached. Numerous yellowish nodules were seen under the serosa, but none penetrated it. Many hemorrhagic and mucinous foci were also seen. The tubes showed acute inflammation in an early stage. A diagnosis of metastatic carcinoma, so-called Krukenberg tumor, was made. Fortunately permission for autopsy was granted. The following pathologic report is a condensation of the report of Dr. Korkosz, assistant pathologist at the Ellis Hospital:

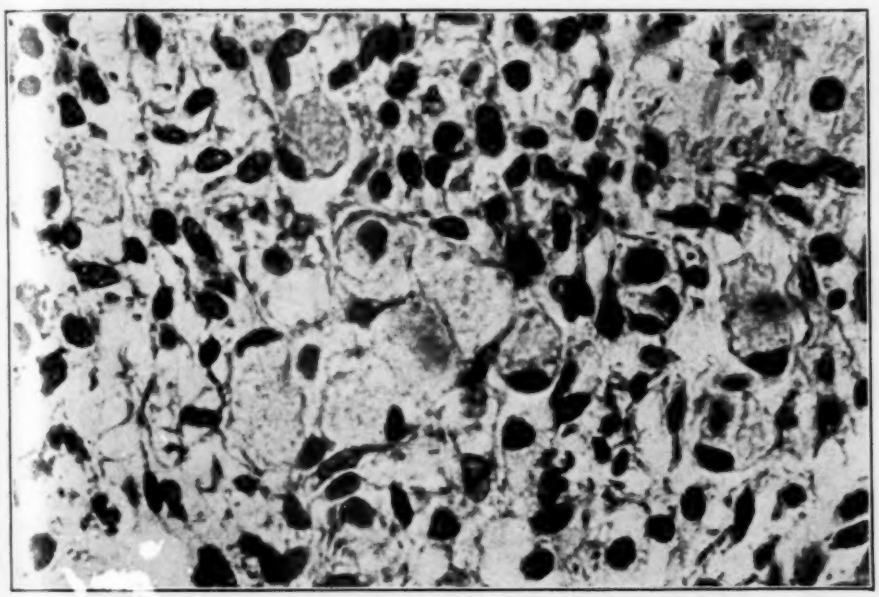

Fig. 2.—Photomicrograph of a section of ovary, showing characteristic "signet-ring" cells; × 80.

Examination of the peritoneum disclosed about 300 cc. of turbid yellow fluid in the cul-de-sac and right gutter. The peritoneum overlying the rectum was markedly injected and dull. The remainder, however, was of normal color and luster except that of the right half of the diaphragm, which was covered by numerous flecks of fibrin. No adhesions were present. The appendix appeared normal. The mesenteric nodes were palpable.

No fluid was present in either pleural cavity. A single dense fibrous band was separated with difficulty in the midportion of the left lung laterally.

The lower half of the left lung was markedly congested. The cut surfaces were dark red. The entire lung exuded considerable pink thin frothy fluid.

Slight crepitus was elicited over the upper half of the lung. The right lung resembled the left.

The pericardial sac contained about 20 cc. of clear yellow fluid. The pericardium appeared normal.

The heart, spleen, pancreas and gallbladder were normal.

The liver was not enlarged; it was pale brown, and its surfaces were smooth. Two white nodules 0.5 cm. in diameter were present on the convex surface of the right lobe. Their cut surfaces were grayish white and smooth. They were sharply delimited from the liver tissue. The cut surfaces of the liver throughout were slightly paler than normal. The lobules were distinct and appeared congested. There was no evidence of neoplasm within the liver.

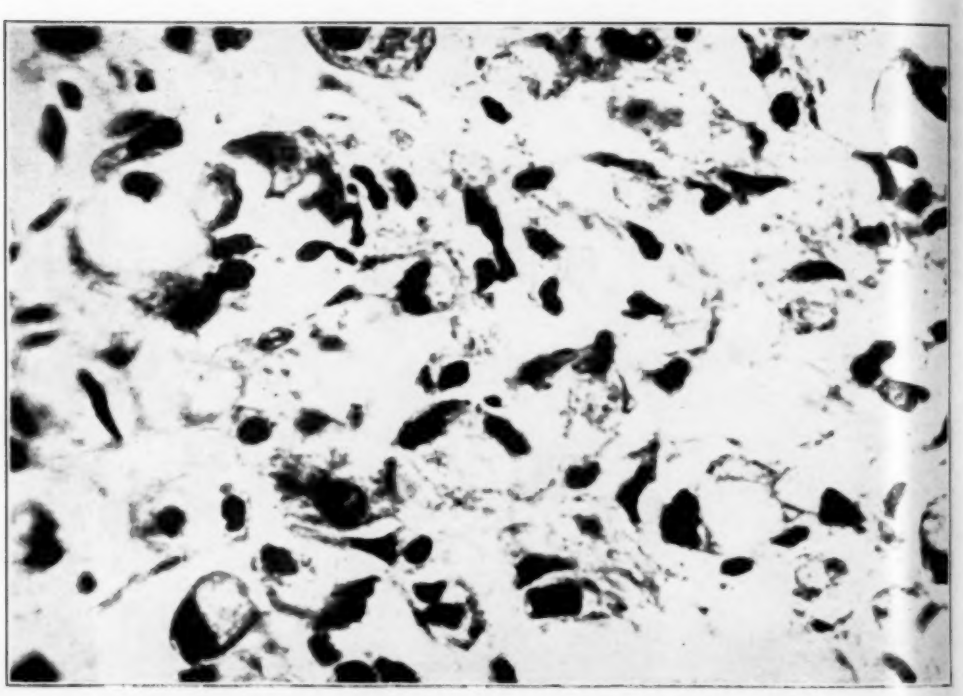

Fig. 3.—Photomicrograph of a section of ovary showing Krukenberg tumor; × 400. The primary lesion was in the stomach.

The stomach was markedly dilated with gas. It also contained about 200 cc. of foul-smelling brown fluid. The mucosa showed occasional small hemorrhagic foci. An oval ulcer 2 by 1 cm. was seen on the greater curvature, near the fundus. (This ulcer was on the posterior wall of the stomach and was not palpable; it was not found until the stomach was removed and opened [C. W. W.]). The edges were firm and slightly elevated. The floor of the ulcer was smooth; the serosa opposite the ulcer appeared normal. The small intestine was moderately distended. The large intestine was markedly distended with gas. The serosa overlying the rectum and a portion of the sigmoid flexure showed many firm, flat yellow plaques. The mesosigmoid contained many firm nodules which averaged 1 cm. in diameter and the cut surfaces of which were smooth and gray. None of the nodules were sharply outlined. Many similar nodules were found

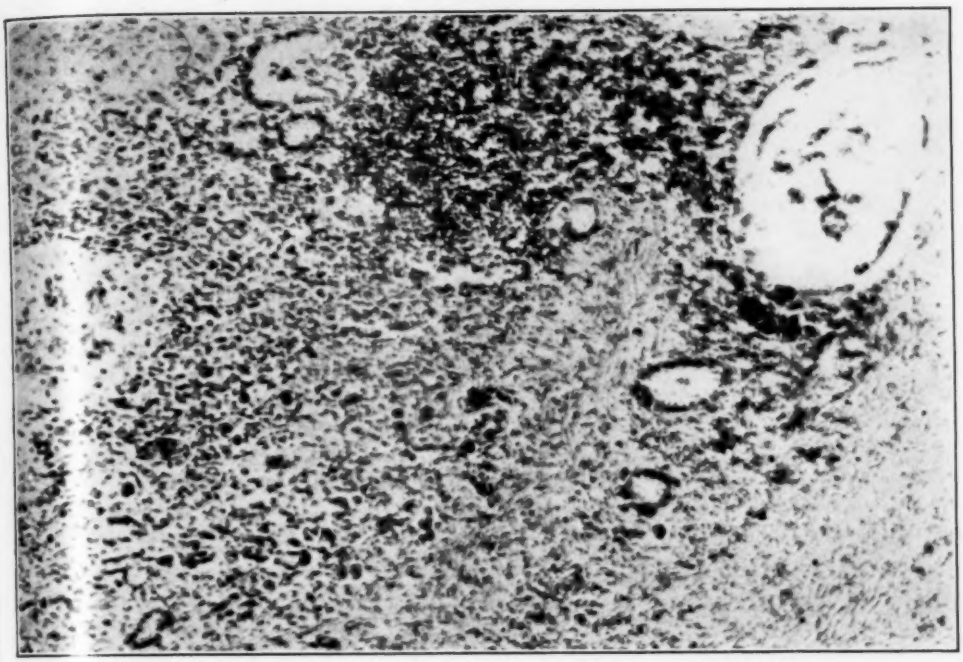

Fig. 4.—Photomicrograph of a section of gastric carcinoma; × 150. Note the infiltrated mucosa and the deep lying tumor acini. Metastases to the ovaries occurred.

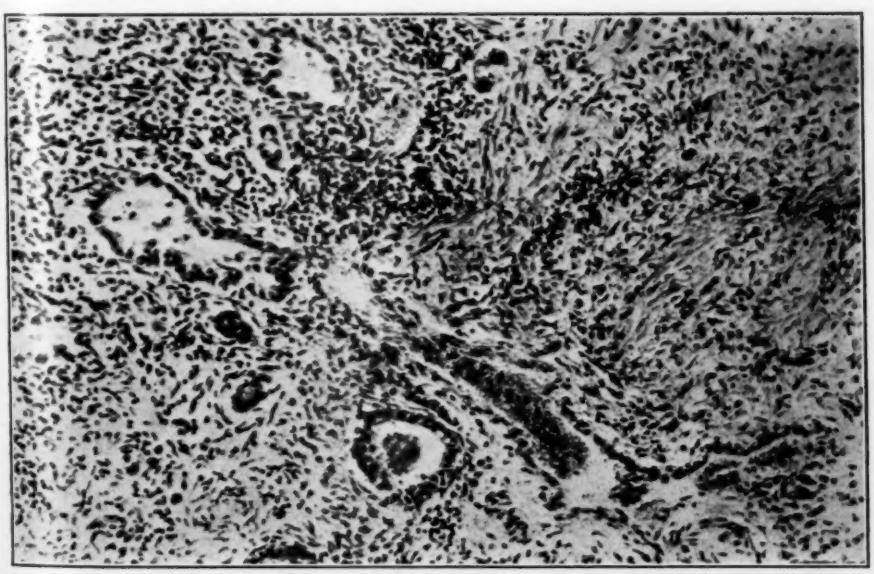

Fig. 5.—Photomicrograph of a section of gastric carcinoma; × 300. Note the tumor acini invading the muscle coat.

in the mesentery. The largest was about 2 cm. in diameter and was found adjacent to the greater curvature of the stomach, near the ulcer which has been mentioned. It was fairly well delimited from the surrounding fatty tissues. The mucosa of the large and small intestine showed nothing of note.

The adrenal glands, the kidneys and the uterus were normal.

The left ovary measured 6 by 3.5 by 3 cm. Several firm nodules were palpable. On section, these were grayish white, with smooth surfaces. Several follicular cysts and corpora lutea were also present.

The anatomic diagnosis was as follows: carcinoma of the fundus of the stomach; metastatic carcinoma of the ovaries, the intestine, the omentum, the liver, the lung and the diaphragm; early acute pelvic peritonitis; acute subdiaphragmatic inflammation (?); edema of the lungs, and acute dilatation of the stomach and intestine. (What was thought to be acute subdiaphragmatic inflammation was later found to be a layer of connective tissue embedded with neoplastic cells and not an inflamed process due to infection.)

Bacteriologic Study.—A smear of the peritoneal fluid showed a few large round mononuclear and occasional polymorphonuclear leukocytes, occasional erythrocytes, rare gram-positive cocci found in pairs and short chains and rare gram-negative bacilli. A culture of the fluid yielded Bacillus coli and Staphylococcus albus. A culture of the blood in dextrose broth yielded B. coli.

Microscopic Examination.—The alveoli contained many red blood cells, lymphocytes and some large mononuclear cells. Many mononuclear cells contained coarse black granules. The capillaries were congested. Several perivascular lymphatics contained clumps of polygonal cells in which were many atypical mitotic figures.

The nodules described as being on the convex surface of the right lobe of the liver consisted of well defined foci of cells arranged in acini embedded in connective tissue. Slight lymphocytic infiltration was present. The nodule was not encapsulated. Direct invasion among the liver cells was seen. In some places partial destruction of the liver cells was demonstrable. The remainder of the section showed the liver cells to contain many droplets of fat, some of them presenting a "signet-ring" appearance.

That portion of the mucosa of the stomach taken from the elevated margin about the ulcer showed the cells to be extremely variable in size and shape. The staining of the cytoplasm varied in the different cells from red to blue. Great numbers of atypical mitotic figures were seen. Some of the cells were distended with mucin and presented the "signet-ring" appearance. The cells were arranged singly, in strands and in acini, many of which were deformed. Marked invasion of the muscularis was present. Many lymphatics were dilated by clumps of neoplastic cells. Great numbers of the smaller lymphatics contained single tumor cells. Scattered foci of lymphocytes were seen. The floor of the ulcer showed pink granular detritus, scattered neoplastic cells and lymphocytes.

The peritoneal surface had a layer of connective tissue in which were embedded neoplastic cells similar to those seen in the stomach. There was no penetration into the muscles of the diaphragm, but on the upper surface were many tumor cells.

Great numbers of neoplastic cells were present in the fatty tissue of the omentum, forming nodular masses.

There was diffuse infiltration by single large round and oval cells with clear cytoplasm displacing the nucleus to one side. Occasional mitotic figures were seen. There was no tendency to the formation of acini or strands of cells as seen elsewhere.

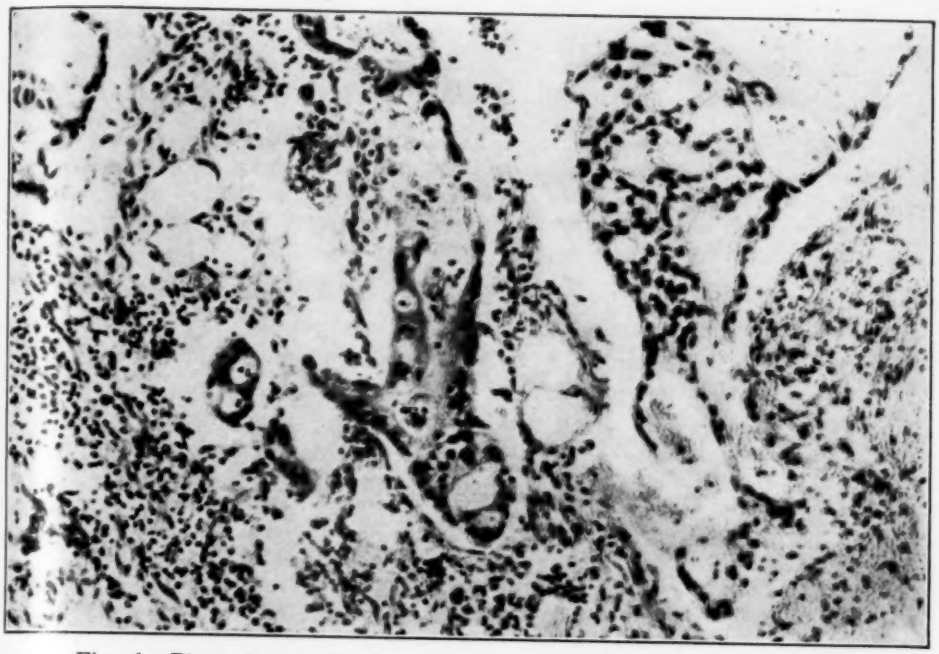

Fig. 6.—Photomicrograph of a section of omentum, showing infiltration by tumor; × 300.

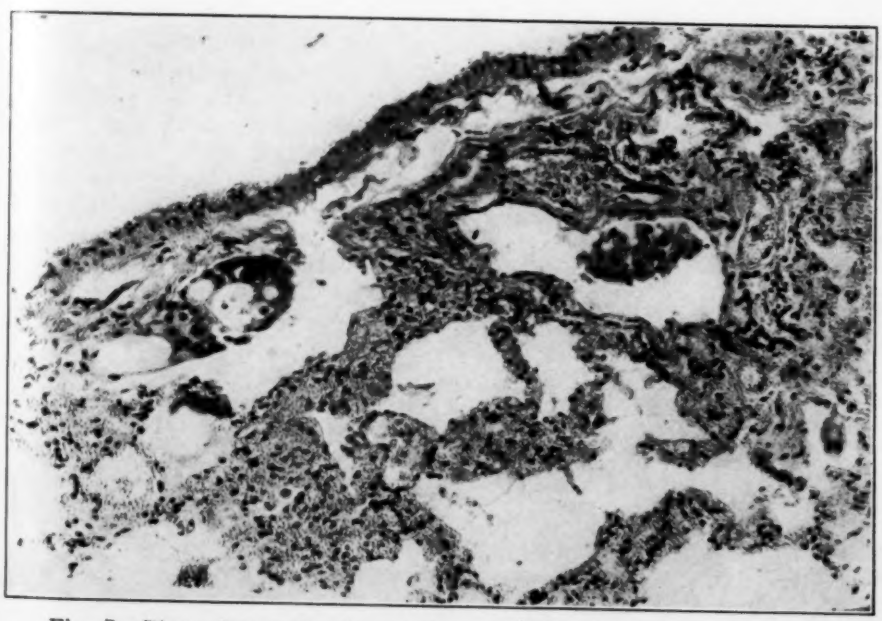

Fig. 7.—Photomicrograph of a section of pulmonary tissue showing tumor cells in the perivascular lymphatics; × 300.

The following is a comment on the autopsy by Dr. Kellert, chief pathologist of the Ellis Hospital:

> Death in this case may be attributed to widely disseminated carcinosis, arising primarily in a small carcinoma of the stomach. Early extension to the ovaries resulted in bilateral carcinoma of those structures, which exhibited the histologic appearance of a typical Krukenberg tumor, which is generally conceded to take orgin in the gastrointestinal tract or accessory organs.

I do not feel that the observations made at autopsy satisfactorily explained the postoperative death in this case any more than those made clinically. From a clinical standpoint, the temperature curve ending in the excessively high temperature of 108 F. was certainly not accounted for by any infection which was discovered. The appearance of the abdomen at autopsy was not that of peritonitis, there being only a slight amount of peritoneal reaction in the pelvis, which might be expected after a laparotomy. The bacteriologic culture of abdominal fluid yielding B. coli is no more than might be expected from postmortem contamination. The rare gram-positive cocci and the rare gram-negative bacilli found in the smears of peritoneal fluid were not, I believe, pathologically significant. It is unfortunate that an autopsy of the brain was not performed, as it is possible that that might have thrown some light on the postoperative picture.